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Anesthesia AND Analgesia

.....CURRENT RESEARCHES

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Journal of the International Anesthesia Research Society

Volume 57, No. 1 January-February, 1978

52nd Congress

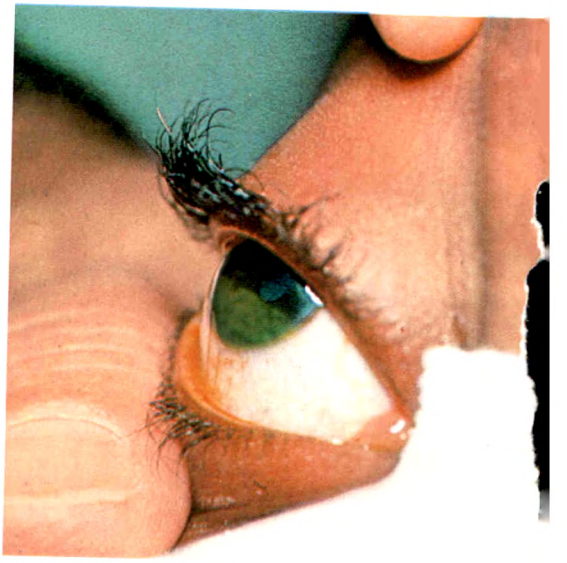
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References: 1. Snow, J.C. et al: Corneal Injuries During General Anesthesia, Anesthesia and Analgesia 54:465 (Jul-Aug) 1975. 2. Terry, H.F. Untoward Ophthalmic and Neurologic Events of Anesthesia, Surg Clin N Amer 45:927 1965. 3. Data on file, Allergan Pharmaceuticals.

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Selected cases for Ketala

There are certain situations where the advantages of Ketalar suggest its serious consideration. Four such hypothetical situations are detailed here.
A fifth hypothetical case illustrates a situation in which Ketalar probably should be used only with caution.



Geriatric surgical procedure

Ketalar offers advantages in minor rectal surgery on elderly patients. When properly administered, Ketalar usually does not depress the patient's blood pressure or pulse rate, which can be a distinct advantage with any patient who is likely to develop hypotension. Further, emergence reactions normally are not a problem with patients in the older age group (over 65).



Severely burned patients

Patients with severe burns—and particularly children—are often excellent cases for Ketalar. In children, Ketalar offers rapid surgical anesthesia (generally within three to four minutes) at a range of 9 to 13 mg/kg, with the effect lasting from 12 to 25 minutes (the time intervals are for IM, not IV). Intramuscular administration avoids the possible difficulty in locating the vein in burn patients (particularly helpful in children where the veins are small). IM administration is also convenient and effective for repeated short-term anesthesia for such procedures as changing burn dressings, and skin grafts.

advancement in anesthesiology **Ketalar** (Ketamine HCl injection) Parke-Davis

Brief summary of prescribing information.

SPECIAL NOTE

EMERGENCE REACTIONS HAVE OCCURRED IN APPROXIMATELY 12% OF PATIENTS.

THE PSYCHOLOGICAL MANIFESTATIONS VARY IN SEVERITY BETWEEN PLEASANT, DREAMLIKE STATES, VIVID IMAGERY, HALLUCINATIONS, AND EMERGENCE DELIRIUM. IN SOME CASES, THESE STATES HAVE BEEN ACCOMPANIED BY CONFUSION, EXCITEMENT, AND IRRATIONAL BEHAVIOR WHICH A FEW PATIENTS RECALL AS AN UNPLEASANT EXPERIENCE. THE DURATION ORDINARILY LASTS NO MORE THAN A FEW HOURS; IN A FEW CASES, HOWEVER, RECURRENCES HAVE TAKEN PLACE UP TO 24 HOURS POSTOPERATIVELY. NO RESIDUAL PSYCHOLOGICAL EFFECTS ARE KNOWN TO HAVE RESULTED FROM USE OF KETALAR.

THE INCIDENCE OF THESE EMERGENCE PHENOMENA IS LEAST IN THE YOUNG (15 YEARS OF AGE OR LESS) AND ELDERLY (OVER 65 YEARS OF AGE) PATIENT. ALSO, THEY ARE LESS FREQUENT WHEN THE DRUG IS GIVEN INTRAMUSCULARLY.

THESE REACTIONS MAY BE REDUCED IF VERBAL, TACTILE, AND VISUAL STIMULATION OF THE PATIENT IS MINIMIZED DURING THE RECOVERY PERIOD. THIS DOES NOT PRECLUDE THE MONITORING OF VITAL SIGNS. IN ADDITION, THE USE OF A SMALL HYPNOTIC DOSE OF A SHORT-ACTING OR ULTRASHORT-ACTING BARBITURATE MAY BE REQUIRED TO TERMINATE A SEVERE EMERGENCE REACTION. THE INCIDENCE OF EMERGENCE REACTIONS IS REDUCED AS EXPERIENCE WITH THE DRUG IS GAINED.

WHEN KETALAR IS USED ON AN OUTPATIENT BASIS, THE PATIENT SHOULD NOT BE RELEASED UNTIL RECOVERY FROM ANESTHESIA IS COMPLETE AND THEN SHOULD BE ACCOMPANIED BY A RESPONSIBLE ADULT.

INDICATIONS

Ketalar (ketamine HCl injection) is recommended:

1. as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketalar is best suited for short procedures but it can be used, with additional doses, for longer procedures;

2. for the induction of anesthesia prior to the administration of other general anesthetic agents;

3. to supplement low-potency agents, such as nitrous oxide.

CONTRAINDICATIONS

Ketamine hydrochloride is contraindicated in those in whom a significant elevation of blood pressure would constitute a serious hazard and those who have shown hypersensitivity to the drug.

WARNINGS

1. Ketalar should be used by or under the direction of physicians experienced in administering general anesthetics and in maintenance of an airway and in the control of respiration.

2. Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.

3. Barbiturates and Ketalar, being chemically incompatible because of precipitate formation, *should not* be injected from the same syringe.

4. Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketalar.

5. Postoperative confusional states may occur during the recovery period.

6. Respiratory depression may occur with overdosage or too rapid a rate of administration of Ketalar, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

Usage in Pregnancy

Since the safe use in pregnancy, including obstetrics (either vaginal or abdominal delivery), has not been established, such use is not recommended.

PRECAUTIONS

1. Because pharyngeal and laryngeal reflexes are usually active, Ketalar (ketamine HCl injection) should not be used alone in surgery or diagnostic procedures of the pharynx, larynx, or bronchial tree. Mechanical stimulation of the pharynx should be avoided, whenever possible, if Ketalar is used alone. Muscle relaxants, with proper attention to respiration, may be required in both of these instances.

2. Resuscitative equipment should be ready for use.

3. ***The incidence of emergence reactions may be reduced*** if verbal and tactile stimulation of the patient is minimized during the recovery period. This does not preclude the monitoring of vital signs (see Special Note).

4. The intravenous dose should be administered over a period of 60 seconds. More rapid administration may result in respiratory depression or apnea and enhanced pressor response.

5. In surgical procedures involving visceral pain pathways, Ketalar should be supplemented with an agent which obtunds visceral pain.

6. Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient.

7. An increase in cerebrospinal fluid pressure has been reported following administration of ketamine hydrochloride. Use with extreme caution in patients with preanesthetic elevated cerebrospinal fluid pressure.

ADVERSE REACTIONS

Cardiovascular: Blood pressure and pulse rate are frequently elevated following administration of Ketalar. However, hypotension

(ketamine HCl inj) . . . and a caution



anipulative diagnostic procedure

Ketalar facilitates diagnostic procedures in which the patient must b moved freely, and in which the n intenance of unaided respiration is essential. The pneumoencephalogram is an example. Once anesthesia is established, the patient can be tr nsferred from a supine to an u. ight, supported position with ease since Ketalar maintains adequate unaided respiration, and there is minimal relaxation of the skeletal muscles.



Emergency room treatment

A good case for Ketalar can be made for use in accident victims with unknown medical histories brought to the emergency room. In the absence of positive medical history, Ketalar can be a useful agent because of its wide margin of safety. Consideration should be given to the effects of a significant increase in blood pressure, hypersensitivity to the drug, and an elevation in cerebrospinal fluid pressure. Ketalar also provides the benefit of rapid onset, and decreases the chance of aspiration because of active laryngeal-pharyngeal reflexes.



A caution:

Caution should be exercised when administering Ketalar to patients who are known to be alcoholics or who are acutely alcohol-intoxicated as such patients may be prone to untoward reactions.

---

a bradycardia have been observed. A ythmia has also occurred.

Re piration: Although respiration is frequently stimulated, severe depression of espiration or apnea may occur following apid intravenous administration of high doses of Ketalar (ketamine HCl injection). L ryngospasms and other forms of airway obstruction have occurred during Ketalar anesthesia.

Eye: Diplopia and nystagmus have been n ed following Ketalar administration. It may cause a slight elevation in intra- pressure measurement.

chological: (See Special Note).

Neurological: In some patients, enhanced skeletal muscle tone may be manifested by nic and clonic movements sometimes esembling seizures (see Dosage and Administration).

Gastrointestinal: Anorexia, nausea and vo ting have been observed; however this is n t usually severe and allows the great of patients to take liquids by mouth ter regaining consciousness age and Administration).

Local pain and exanthema at the site have infrequently been re- nsient erythema and/or morbilli- ave also been reported.

AND ADMINISTRATION

ve Preparations:

miting has been reported following ministration, airway protection is orded because of active laryngeal- reflexes. However, since these ay also be diminished by supple- nesthetics or muscle relaxants, the ty of aspiration must be considered. talar is recommended for use in the patient whose stomach is not empty when, in the judgment of the practitioner, the benefits the drug outweigh the possible risks.

Atropine, scopolamine, or other drying nt should be given at an appropriate rval prior to induction.

Dosage

As with other general anesthetic agents, the individual response to Ketalar (ketamine HCl injection) is somewhat varied depending on the dose, route of administration, and age of patient, so that dosage recommendation cannot be absolutely fixed. The drug should be titrated against the patient's requirements.

Onset and Duration:

Because of rapid induction following the initial intravenous injection, the patient should be in a supported position during administration.

The onset of action of Ketalar (ketamine HCl injection) is rapid; an intravenous dose of 2 mg/kg (1 mg/lb) of body weight usually produces surgical anesthesia within 30 seconds after injection, with the anesthetic effect usually lasting five to ten minutes. If a longer effect is desired, additional increments can be administered intravenously or intramuscularly to maintain anesthesia without producing significant cumulative effects.

Intramuscular doses, from experience primarily in children, in a range of 9 to 13 mg/kg (4 to 6 mg/lb) usually produce surgical anesthesia within three to four minutes following injection, with the anesthetic effect usually lasting 12 to 25 minutes.

Induction:

Intravenous Route: The initial dose of Ketalar administered intravenously may range from 1 mg/kg to 4.5 mg/kg (0.5 to 2 mg/lb). The average amount required to produce five to ten minutes of surgical anesthesia has been 2 mg/kg (1 mg/lb).

NOTE: The 100 mg/ml concentration (S-V 1585) of Ketalar, *should not* be injected intravenously without proper dilution. It is recommended the drug be diluted with an equal volume of either Sterile Water for Injection, USP, Normal Saline, or 5% Dextrose in Water.

Rate of Administration: It is recommended that Ketalar be administered slowly (over a period of 60 seconds). More rapid administration may result in respiratory depression and enhanced pressor response.

Intramuscular Route: The initial dose of Ketalar administered intramuscularly may range from 6.5 to 13 mg/kg (3 to 6 mg/lb). A dose of 10 mg/kg (5 mg/lb) will usually produce 12 to 25 minutes of surgical anesthesia.

Maintenance of Anesthesia:

Increments of one half to the full induction dose may be repeated as needed for maintenance of anesthesia. However, it should be noted that purposeless and tonic-clonic movements of extremities may occur during the course of anesthesia. These movements do not imply a light plane and are not indicative of the need for additional doses of the anesthetic.

It should be recognized that the larger the total dose of Ketalar (ketamine HCl injection) administered, the longer will be the time to complete recovery.

Supplementary Agents:

Ketalar is clinically compatible with the commonly used general and local anesthetic agents when an adequate respiratory exchange is maintained.

HOW SUPPLIED

Ketalar is supplied as the hydrochloride in concentrations equivalent to ketamine base.

N 0071-4581-15—Each 50-ml vial contains 10 mg/ml. Supplied in cartons of 10.

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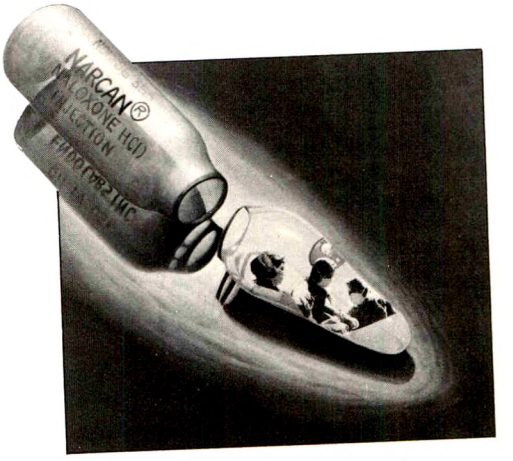
NARCAN® reverses narcotic-induced respiratory depression

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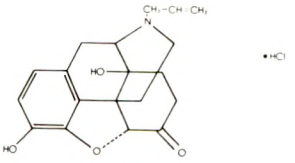
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OF NARCOTIC-SUPPLEMENTED ANESTHES

NARCAN®
naloxone HCl

DESCRIPTION NARCAN* (naloxone hydrochloride), a narcotic antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.



NALOXONE HYDROCHLORIDE
(-)-17-Allyl-4, 5α-epoxy-3, 14-
dihydroxymorphinan-6-one hydrochloride

Naloxone hydrochloride occurs as slightly off-white crystals, and is soluble in water, slightly soluble in alcohol and practically insoluble in ether.

NARCAN® (naloxone hydrochloride) Injection is available in two concentrations, 0.02 mg and 0.4 mg of naloxone hydrochloride per ml. Each ml of either strength contains 8.6 mg of sodium chloride; and 2.0 mg of methylparaben and propylparaben as preservatives in a ratio of 9 to 1. pH is adjusted with hydrochloric acid.

ACTIONS NARCAN* (naloxone hydrochloride) is an essentially pure narcotic antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other narcotic antagonists; NARCAN* (naloxone hydrochloride) does not produce respiratory depression, psychotomimetic effects or pupillary constriction. In the absence of narcotics or agonistic effects of other narcotic antagonists it exhibits essentially no pharmacologic activity.

In the presence of physical dependence on narcotics NARCAN* (naloxone hydrochloride) will produce withdrawal symptoms; it has not been shown to produce tolerance nor to cause physical or psychological dependence.

When NARCAN* (naloxone hydrochloride) is administered intravenously the onset of action is generally apparent within two minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration of NARCAN* (naloxone hydrochloride). Intramuscular administration produces a more prolonged effect than intravenous administration. The requirement for repeat doses of NARCAN* (naloxone hydrochloride), however, will also be dependent upon the amount, type and route of administration of the narcotic being antagonized.

INDICATIONS NARCAN* (naloxone hydrochloride) is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by natural and synthetic narcotics, propoxyphene and the narcotic-antagonist analgesic pentazocine. NARCAN* (naloxone hydrochloride) is also indicated for the diagnosis of suspected acute opiate overdosage.

CONTRAINDICATIONS NARCAN* (naloxone hydrochloride) is contraindicated in patients known to be hypersensitive to it.

WARNINGS NARCAN* (naloxone hydrochloride) should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

The patient who has satisfactorily responded to NARCAN* (naloxone hydrochloride) should be kept under continued surveillance and repeated doses of NARCAN* (naloxone hydrochloride) should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN* (naloxone hydrochloride).

NARCAN* (naloxone hydrochloride) is not effective against respiratory depression due to non-opioid drugs.

Usage in Pregnancy Safe use of NARCAN* (naloxone hydrochloride) during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or other embryotoxic effects (See ANIMAL PHARMACOLOGY AND TOXICOLOGY). However, NARCAN* (naloxone hydrochloride) should be administered to pregnant patients only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS In addition to NARCAN* (naloxone hydrochloride), other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning.

In an isolated report two patients with pre-existing ventricular irritability requiring lidocaine, and either isoproterenol or epinephrine for hypotension following cardiopulmonary bypass procedures, developed ventricular tachycardia or fibrillation when given NARCAN* (naloxone hydrochloride) I.V. at 9 and 14 hours, respectively, postoperatively for persistent unresponsiveness. Although a direct cause and effect relationship has not been established, NARCAN* (naloxone hydrochloride) should be used with caution in patients with cardiac irritability.

ADVERSE REACTIONS In rare instances nausea and vomiting have been reported in postoperative patients receiving NARCAN* (naloxone hydrochloride) in doses higher than that recommended; a cause and effect relationship has not been established.

DOSAGE AND ADMINISTRATION NARCAN* (naloxone hydrochloride) may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of NARCAN* (naloxone hydrochloride) the patient should be kept under continued surveillance and repeated doses of NARCAN* (naloxone hydrochloride) should be administered, as necessary.

USAGE IN ADULTS Narcotic Overdose—Known or Suspected The usual initial adult dose is 0.4 mg (1 ml) NARCAN* (naloxone hydrochloride) administered I.V., I.M. or S.C. If the desired degree of counteraction and improvement in respiratory function is not obtained immediately following I.V. administration, it may be repeated intravenously at 2 to 3 minute intervals. Failure to obtain significant improvement after 2 or 3 doses suggests that the condition may be due partly or completely to other disease processes or non-opioid drugs.

Post Operative Narcotic Depression For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of NARCAN* (naloxone hydrochloride) are usually sufficient. The dose of NARCAN* (naloxone hydrochloride) should be titrated according to the patient's response. Excessive dosage of NARCAN* (naloxone hydrochloride) may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or tachycardia.

For the initial reversal of respiratory depression, NARCAN* (naloxone hydrochloride) should be injected in increments of 0.1 to 0.2 mg intravenously at two to three minute intervals to the desired degree of reversal i.e., adequate ventilation and alertness without significant pain or discomfort.

Repeat doses of NARCAN* (naloxone hydrochloride) may be required within one to two hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

USAGE IN CHILDREN Narcotic Overdose—Known or Suspected The usual initial child dose is 0.01 mg/kg body weight given I.V., I.M. or S.C. This dose may be repeated in accordance with the adult administration guideline. If necessary, NARCAN* (naloxone hydrochloride) can be diluted with sterile water for injection.

USAGE IN NEONATES Narcotic-induced depression The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M. or S.C. This dose may be repeated in accordance with adult administration guidelines.

HOW SUPPLIED 0.4 mg/ml of NARCAN* (naloxone hydrochloride) for intravenous, intramuscular and subcutaneous administration.

Available in 1 ml ampuls in boxes of 10 and 100.

0.02 mg/ml of NARCAN* (naloxone hydrochloride) NEONATAL INJECTION for intravenous, intramuscular and subcutaneous administration.

Available in 2 ml ampuls in boxes of 10 and 100 ampuls.

ANIMAL PHARMACOLOGY AND TOXICOLOGY In the mouse and rat the intravenous LD_{50} is 150 ± 5 mg/kg and 109 ± 4 mg/kg respectively. In acute subcutaneous toxicity studies in newborn rats the LD_{50} (95% CL) is 260 (228-296) mg/kg. Subcutaneous injection of 100 mg/kg/day in rats for 3 weeks produced only transient salivation and partial ptosis following injections; no toxic effects were seen at 10 mg/kg/day for 3 weeks.

Reproductive studies including fertility, general reproductive performance, embryotoxicity, teratogenicity, and lactation did not show any abnormality in mice and rats at 10 mg/kg/day.

Endo Laboratories, Inc.
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

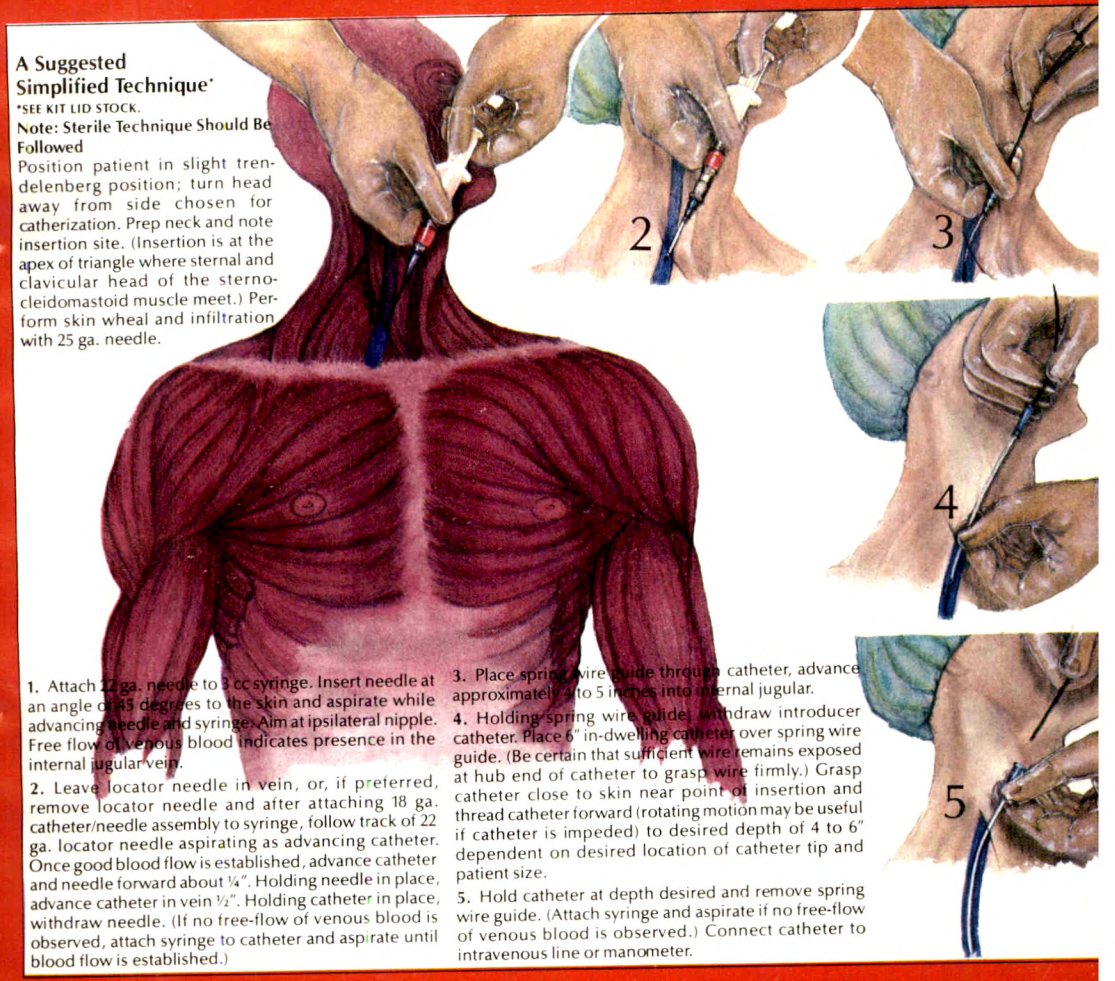
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EDO-050N

May, 1977

ARROW
INTERNAL JUGULAR PUNCTURE KIT
WITH 16 GAUGE IN-DWELLING CATHETER
ARROW PEDIATRIC INTERNAL JUGULAR PUNCTURE KIT
WITH 20 GAUGE IN-DWELLING CATHETER

STERILE • DISPOSABLE • NO MEDICATION



A Suggested Simplified Technique*

*SEE KIT LID STOCK.

Note: Sterile Technique Should Be Followed

Position patient in slight trendelenberg position; turn head away from side chosen for catherization. Prep neck and note insertion site. (Insertion is at the apex of triangle where sternal and clavicular head of the sternocleidomastoid muscle meet.) Perform skin wheal and infiltration with 25 ga. needle.

1. Attach 22 ga. needle to 3 cc syringe. Insert needle at an angle of 45 degrees to the skin and aspirate while advancing needle and syringe. Aim at ipsilateral nipple. Free flow of venous blood indicates presence in the internal jugular vein.

2. Leave locator needle in vein, or, if preferred, remove locator needle and after attaching 18 ga. catheter/needle assembly to syringe, follow track of 22 ga. locator needle aspirating as advancing catheter. Once good blood flow is established, advance catheter and needle forward about ¼". Holding needle in place, advance catheter in vein ½". Holding catheter in place, withdraw needle. (If no free-flow of venous blood is observed, attach syringe to catheter and aspirate until blood flow is established.)

3. Place spring wire guide through catheter, advance approximately 4 to 5 inches into internal jugular.

4. Holding spring wire guide, withdraw introducer catheter. Place 6" in-dwelling catheter over spring wire guide. (Be certain that sufficient wire remains exposed at hub end of catheter to grasp wire firmly.) Grasp catheter close to skin near point of insertion and thread catheter forward (rotating motion may be useful if catheter is impeded) to desired depth of 4 to 6" dependent on desired location of catheter tip and patient size.

5. Hold catheter at depth desired and remove spring wire guide. (Attach syringe and aspirate if no free-flow of venous blood is observed.) Connect catheter to intravenous line or manometer.

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Arrow International has developed an Internal Jugular Puncture Kit that carefully matches component sizes and aggregates them in one efficient, sterile, disposable, procedure kit.

FEATURES: 18 Gauge Thin Wall Catheter over 20 Gauge Introducer Needle—A perfectly matched thin wall catheter and needle sized to pass .035" spring wire guide. **.035 Spring Wire Guide**—A pliable, stainless steel spring wire guide with soft-tip at both ends. **16 Gauge x 6" Teflon* In-Dwelling Catheter**—A radiopaque 6" (15.24cm) in-dwelling catheter with large lumen for excellent flow rates.

*Teflon is a registered trademark of E.I. DuPont de Nemours & Co. for DuPont fluorocarbon resins.

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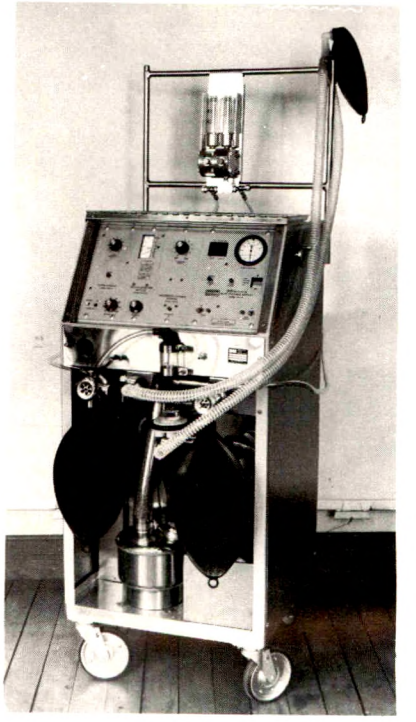
EMERSON IMV Ventilator

Intermittent Mandatory Ventilation

Continuous-flow voluntary ventilation, with intermittent forced breaths, is an alternative to assisted or controlled respiration. It has been found especially valuable for infants and for use in "weaning" adults as they improve.

Air fully humidified (and usually enriched with oxygen) flows continuously to a reservoir bag, and is available for unobstructed inspiration by the patient. A slight expiratory back-pressure (PEEP) may be added, to keep the lungs expanded. At intervals the ventilator delivers a "mandatory" breath, which supplements the patient's own breathing activity and increases minute volume. The machine does not have to "take over". The patient maintains his own homeostasis, without interference from drugs or hyperventilation.[1]

At first the ventilator is generally set to supply mandatory breaths at a normal controlled rate. This controlled respiration is then gradually changed, by lengthening the interval between breaths (a second or two at a time) as the patient's condition improves. Eventually mandatory breaths are spaced so far apart that the patient scarcely relies on them at all — and "weaning" is completed.[2]



VERSUS ASSIST

Triggering an assistor has often been a problem, particularly for infants, since their rates are rapid and their inspiratory impulses are slight. If synchronization is less than perfect, the patient inhales (at least part of the time) with no fresh gas available. Under such circumstances, blood levels of CO_2 rise, as noted by Kirby and associates.[1]

VERSUS CONTROL

For apneic patients, control is obviously needed. But to take over, when a patient is breathing spontaneously, drugs have to be used or the patient has to be hyperventilated. Either procedure has drawbacks. Paralytic or sedative agents may obscure signs of neurological or metabloic disorders. Lowered muscle tone may impair venous return, and hence cardiac output. The effects of such drugs are particularly hard to predict in infants.

Hyperventilation (often used to suppress spontaneous breathing efforts) has drawbacks, too. The resultant alkalosis reduces cerebral blood flow. Blood levels of calcium and magnesium are altered. Airway resistance increases and pulmonary compliance decreases with hypocarbia.[3] Finally, there is evidence of a shift in the carbon dioxide response curve, which makes weaning more difficult.

All of these pit-falls can be avoided by using continuous-flow IMV.

Please request Form 3-MV.

J. H. EMERSON COMPANY

CAMBRIDGE, MASSACHUSETTS 02140

Now, an anticholinergic for use in anesthesia with significant advantages over atropine...

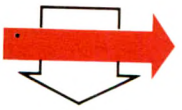
Robinul® Injectable

(Glycopyrrolate Injection, NF)



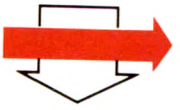
- Little or no CNS effect
- Prolonged vagal blocking effe
- Longer antisialagogue activity

See last page for



PRE-OPERATIVELY

- Protects against excessive pharyngeal and bronchial secretions.
- Protects against excessive volume and acidity of gastric secretions—a danger if pulmonary aspiration occurs.
- Protects against vagal reflexes at time of intubation.



INTRA- OR POST-OPERATIVELY

- Protects against arrhythmias and bradycardia associated with drugs used for reversal of muscle relaxants (e.g. neostigmine).
- Protects against surgically-induced vagal reflexes.

Robinul® Injectable (Glycopyrrolate Injection, NF)
an anticholinergic with significant advantages over atropine

ituation	Objective	Action
reoperative	Reduction of gastric secretions plus elevation of gastric pH above 2.5 to help protect against serious sequelae of aspiration.	Use Robinul Injectable in the premedication regimen.
duction of nesthesia	To have unobstructed view of glottis prior to tracheal intubation. To help protect against vagal reflexes during intubation.	Use Robinul Injectable in the premedication regimen.
tra- perative	To help protect against surgically or drug induced vagal reflexes.	Use Robinul Injectable intraoperatively.
ost- perative	To help prevent excess peripheral muscarinic effects of cholinergic agents used in the reversal regimen.	Use Robinul Injectable in the reversal regimen.
covery om	To help prevent "central anticholinergic syndrome."	Use Robinul Injectable whenever an anticholinergic is used.

Each 1 ml contains:

Glycopyrrolate, NF	0.2 mg
Water for Injection, USP	q.s.
Chlorobutanol, USP (preservative)	0.5%

For intramuscular or intravenous administration in conjunction with anesthesia.

Contraindications: There are no absolute contraindications to the use of Robinul Injectable in conjunction with anesthesia except known hypersensitivity to glycopyrrolate.

Warnings: This drug should be used with great caution, if at all, in patients with glaucoma or asthma.

Precautions: ***Usage in Pregnancy.*** The use of any drug in pregnancy, lactation, or in the childbearing age requires that the potential benefits of the drug be weighed against the possible hazards to mother and child. Reproduction studies in rats and rabbits revealed no teratogenic effects from glycopyrrolate. However, diminished rates of conception and of survival at weaning were observed in rats, in a dose-related manner. Studies in dogs suggest that this may be due to diminished seminal secretion which is evident at high doses of glycopyrrolate.

Use with caution in patients with: myasthenia gravis; coronary artery disease; congestive heart failure; cardiac arrhythmias; hypertension.

The intravenous administration of any anticholinergic in the presence of cyclopropane anesthesia can result in ventricular arrhythmias; therefore, caution should be observed if Robinul (glycopyrrolate) Injectable must be used during cyclopropane anesthesia. If the drug is given in small incremental doses of 0.1 mg or less, the likelihood of producing ventricular arrhythmias is reduced.

Investigate any tachycardia before giving glycopyrrolate since an increase in the heart rate may occur.

Adverse Reactions: Anticholinergics produce certain effects most of which are extensions of their fundamental pharmacological actions. Adverse reactions to anticholinergics in general may include dry mouth; urinary hesitancy and retention; blurred vision due to mydriasis; increased ocular tension; tachycardia; palpitation; decreased sweating; loss of taste; headache; nervousness; drowsiness; weakness; dizziness; insomnia; nausea; vomiting; impotence; suppression of lactation; constipation; bloated feeling; severe allergic reaction or drug idiosyncrasies including anaphylaxis; urticaria and other dermal manifestation; some degree of mental confusion and/or excitement, especially in elderly persons.

Dosage and Administration: Robinul (glycopyrrolate) Injectable may be administered intramuscularly, or intravenously, without dilution, in the following indications:

Adults: ***Preanesthetic Medication.*** The recommended dose of Robinul (glycopyrrolate) Injectable is 0.002 mg (0.01 ml) per pound of body weight by intramuscular injection, given 30 to 60 minutes prior to the anticipated time of induction of anesthesia or at the time the preanesthetic narcotic and/or sedative are administered.

Intraoperative Medication. Robinul (glycopyrrolate) Injectable may be used during surgery to counteract drug-induced or vagal traction reflexes with the associated arrhythmias (e.g., bradycardia). It should be administered intravenously as single doses of 0.1 mg (0.5 ml) and repeated, as needed, at intervals of 2-3 minutes. The usual attempts should be made to determine the etiology of the arrhythmia, and the surgical or anesthetic manipulations necessary to correct parasympathetic imbalance should be performed.

Reversal of Neuromuscular Blockade. The recommended dose of Robinul (glycopyrrolate) Injectable is 0.2 mg (1.0 ml) for each 1.0 mg (1.0 ml) of neostigmine or the equivalent dose of pyridostigmine. In order to minimize the appearance of cardiac side effects, the drugs may be administered simultaneously by intravenous injection and may be mixed in the same syringe.

Children: ***Preanesthetic Medication.*** The recommended dose of Robinul (glycopyrrolate) Injectable in children up to 12 years of age is 0.002 mg to 0.004 mg (0.01 ml to 0.02 ml) per pound of body weight intramuscularly, given 30 to 60 minutes prior to the anticipated time of induction of anesthesia or at the time the preanesthetic narcotic and/or sedative are administered.

Intraoperative Medication. Because of the long duration of action of Robinul (glycopyrrolate) if used as preanesthetic medication, additional Robinul (glycopyrrolate) Injectable for anticholinergic effect intraoperatively is rarely needed; in the event it is required the recommended pediatric dose is 0.002 mg (0.01 ml) per pound of body weight intravenously, not to exceed 0.5 mg (0.5 ml) in a single dose which may be repeated, as needed at intervals of 2-3 minutes. The usual attempts should be made to determine the etiology of the arrhythmia, and the surgical or anesthetic manipulations necessary to correct parasympathetic imbalance should be performed.

Reversal of Neuromuscular Blockade. The recommended pediatric dose of Robinul (glycopyrrolate) Injectable is 0.2 mg (1.0 ml) for each 1.0 mg (1.0 ml) of neostigmine or the equivalent dose of pyridostigmine. In order to minimize the appearance of cardiac side effects, the drugs may be administered simultaneously by intravenous injection and may be mixed in the same syringe.

Compatibility With Other Agents: ***Known compatibilities.*** Robinul (glycopyrrolate) Injectable is compatible for mixing in injection with the following: 5% and 10% glucose in water; saline; Demerol® (meperidine) Injectable; morphine sulfate; Innovar® (fentanyl plus droperidol) Injectable; Vistaril® (hydroxyzine) Injectable; Prostigmin® (neostigmine) Injectable; Mestinon® (pyridostigmine) Injectable. Robinul Injectable may be administered via the tubing of a running infusion of physiological saline or lactated Ringer's solution.

Known incompatibilities include the following injectables: sodium bicarbonate; Valium® (diazepam); sodium pentobarbital; various phenothiazines; Dramamine® (dimenhydrinate), and chloramphenicol.

Drug Interaction During Anesthesia. Glycopyrrolate has been used clinically with at least the following medications: a barbiturate (sodium thiopental); narcotic analgesics (morphine, alphaprodine hydrochloride, fentanyl); sedative/tranquilizers (droperidol, diazepam); gaseous anesthetics (nitrous oxide); volatile liquid anesthetics (diethyl ether, halothane, methoxyflurane, enflurane); parenteral anesthetics (ketamine); peripherally-acting skeletal muscle relaxants (succinylcholine, gallamine, d-tubocurarine, pancuronium); cholinergic agents (neostigmine, pyridostigmine); and other anticholinergics (atropine).

There are no known unique or unanticipated drug-drug interactions with other agents except that Robinul (glycopyrrolate) Injectable should be used with caution if at all during cyclopropane anesthesia (see Precautions).

Management of Overdosage: To combat peripheral anticholinergic effects, a quaternary ammonium anticholinesterase such as neostigmine methylsulfate may be given in a dose of 1.0 mg for each 1.0 mg of Robinul (glycopyrrolate) Injectable known to have been administered.

How Supplied: Robinul (glycopyrrolate) Injectable is available in 1 ml single dose vials; and 5 ml and 20 ml multiple dose vials (NDC 0031-7890).

Rev. Aug. 1

A.H.Robins Company, Richmond, Va. 23220

A·H·ROBI

for intramuscular or intravenous administration in conjunction with anesthe

Robinul® Injectable

(Glycopyrrolate Injection, NF)

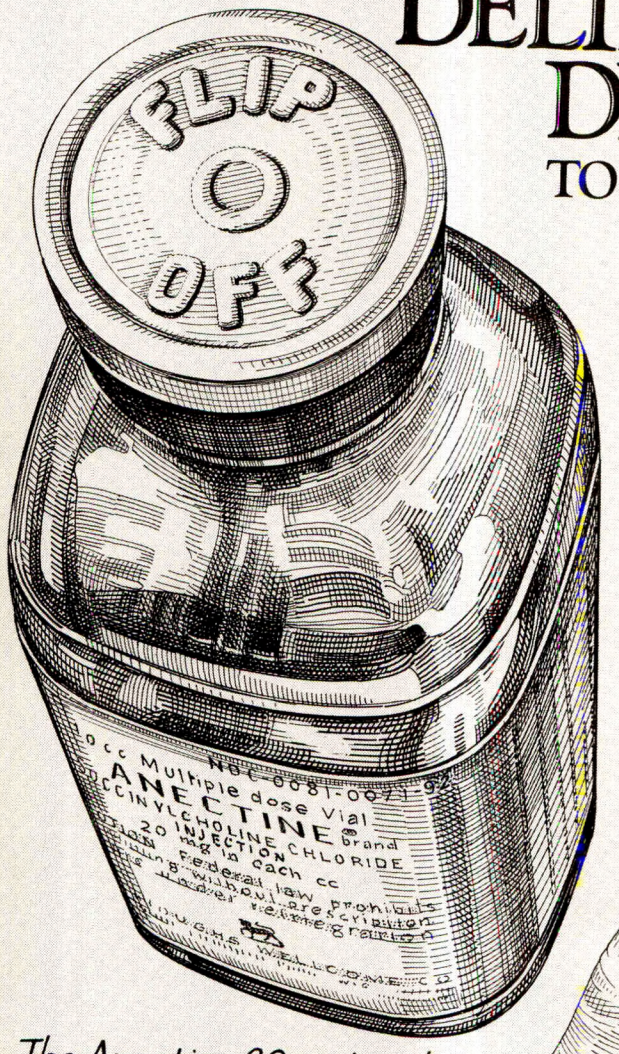
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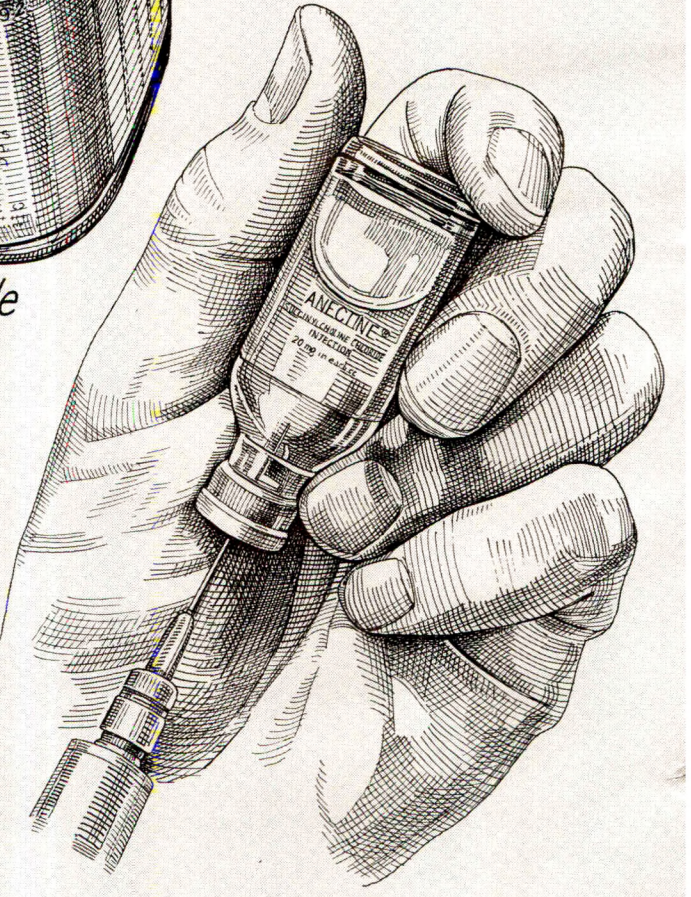
ANECTINE

(succinylcholine chloride)
Packages

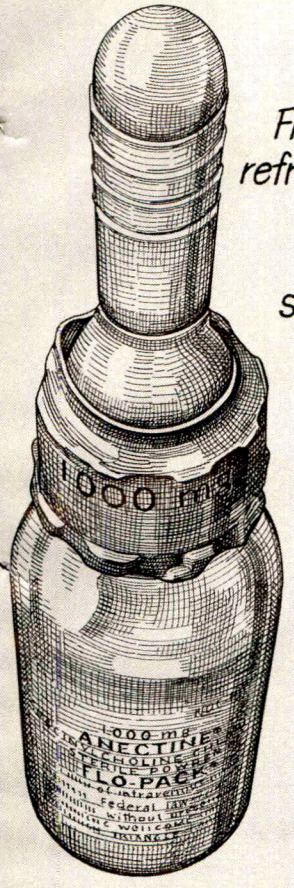
Only Anectine packages offer all these advantages



The Anectine 20 mg bottle is uniquely shaped for added safety and has a convenient flip-off top for speed of use.



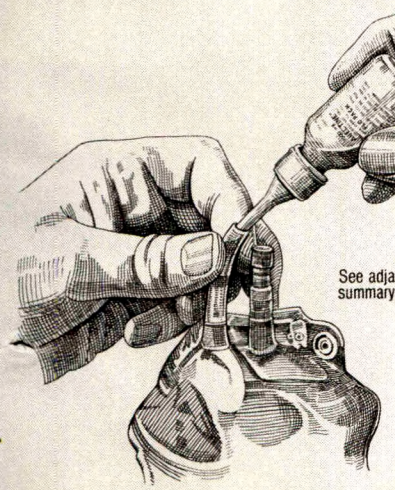
The Anectine 20 mg bottle has a distinctive yellow and red label which can also be read from the reverse side.



The Anectine® Flo-Pack needs no refrigeration. Mixes instantly with diluent. No separate needle or syringe necessary.



The Anectine Flo-Pack in 500 or 1000 mg sizes works with either bottles or bags.



See adjacent column for brief summary of prescribing information.

ANECTINE®
(succinylcholine chloride)

THIS DRUG SHOULD BE USED ONLY BY INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS AND HAZARDS.

CONTRAINDICATIONS: Contraindicated for persons with a known hypersensitivity to the drug.

WARNINGS:

WARNING: SUCCINYLCHOLINE SHOULD BE USED ONLY BY THOSE SKILLED IN THE MANAGEMENT OF ARTIFICIAL RESPIRATION AND ONLY WHEN FACILITIES ARE INSTANTLY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND FOR PROVIDING ADEQUATE VENTILATION OF THE PATIENT, INCLUDING THE ADMINISTRATION OF OXYGEN UNDER POSITIVE PRESSURE AND THE ELIMINATION OF CARBON DIOXIDE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR TO CONTROL RESPIRATION.

Succinylcholine should not be mixed with short-acting barbiturates in the same syringe or administered simultaneously through the same needle. Solutions of succinylcholine have an acid pH whereas those of barbiturates are alkaline in reaction. Depending upon the resultant pH of a mixture of the solutions of these drugs, either free barbituric acid may be precipitated or succinylcholine hydrolyzed.

Usage in pregnancy: Safe use of succinylcholine has not been established with respect to possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential, particularly during early pregnancy, unless, in the physician's judgment, the potential benefits outweigh the unknown hazards.

PRECAUTIONS: Low levels or abnormal variants of plasma cholinesterase may be associated with prolonged respiratory depression or apnea following use of succinylcholine. Low levels of plasma cholinesterase may occur in patients with severe liver disease or cirrhosis, severe anemia, malnutrition, severe dehydration, changes in body temperature, exposure to neurotoxic insecticides or those receiving antimalarial drugs. Succinylcholine should be administered at minimal dosage and with extreme care to such patients. If low plasma cholinesterase is suspected, a small test dose of from 5 to 10 mg of succinylcholine may be administered or relaxation may be produced by cautious administration of a 0.1% solution of the drug by intravenous drip. Drugs which either inhibit plasma cholinesterase such as neostigmine or phospholine iodide, or compete with succinylcholine for the enzyme, as does intravenous procaine, should not be given concurrently.

Succinylcholine should be administered with great caution to patients with severe burns, those recovering from severe trauma, those suffering from electrolyte imbalance, those receiving quinidine, those who have been digitalized recently or who may have digitalis toxicity as serious cardiac arrhythmias or cardiac arrest may result. Patients with pre-existing hyperkalemia or who are paraplegic, have suffered spinal neuraxis injury or have degenerative or dystrophic neuromuscular disease tend to become severely hyperkalemic when succinylcholine is given. Succinylcholine given over a long period of time may change the characteristic depolarization block of the myoneural junction to a nondepolarizing block resulting in prolonged respiratory depression or apnea. In such cases, small repeated doses of neostigmine may possibly act as an antagonist. A peripheral nerve stimulator may be used to determine the type of neuromuscular blockade. If a depolarization block is present, both fast (tetanic) and slow (twitch) rates of nerve stimulation are well-sustained and post-tetanic facilitation is absent. If a nondepolarizing block is present, there is a post-tetanic facilitation and "fade" of successive stimuli on both fast (tetanic) and slow (twitch) rates of nerve stimulation. Succinylcholine should be used with caution during ocular surgery and in patients with glaucoma. Patients with fractures or muscle spasm may suffer additional trauma if fasciculations are induced. Muscle fasciculations and hyperkalemia may be reduced by administering a small dose of a nondepolarizing relaxant. If other relaxants are to be used during the same period, the possibility of a synergistic or antagonistic effect should be considered. In recent years a fulminant syndrome, malignant hyperthermia, has been reported and observed during anesthesia. Its etiology is not fully understood. It occurs in genetically prone individuals of all ages and both sexes receiving potent anesthetics such as halothane, methoxyfluothane, cyclopropane and diethyl ether. It appears to develop irrespective of concomitant use of a muscle relaxant but may be triggered by succinylcholine. Because of the seriousness of malignant hyperthermia and the need for early, effective treatment, continuous monitoring of the patient temperature is suggested.

ADVERSE REACTIONS: Profound and prolonged muscle relaxation may occur, resulting in respiratory depression to the point of apnea. Hypersensitivity to the drug may exist in rare instances. The following adverse reactions have been reported: bradycardia, tachycardia, hypertension, hypotension, arrhythmias, cardiac arrest, prolonged respiratory depression or apnea, hyperthermia, increased intraocular pressure, muscle fasciculation, postoperative muscle pain, myoglobinemia and excessive salivation.

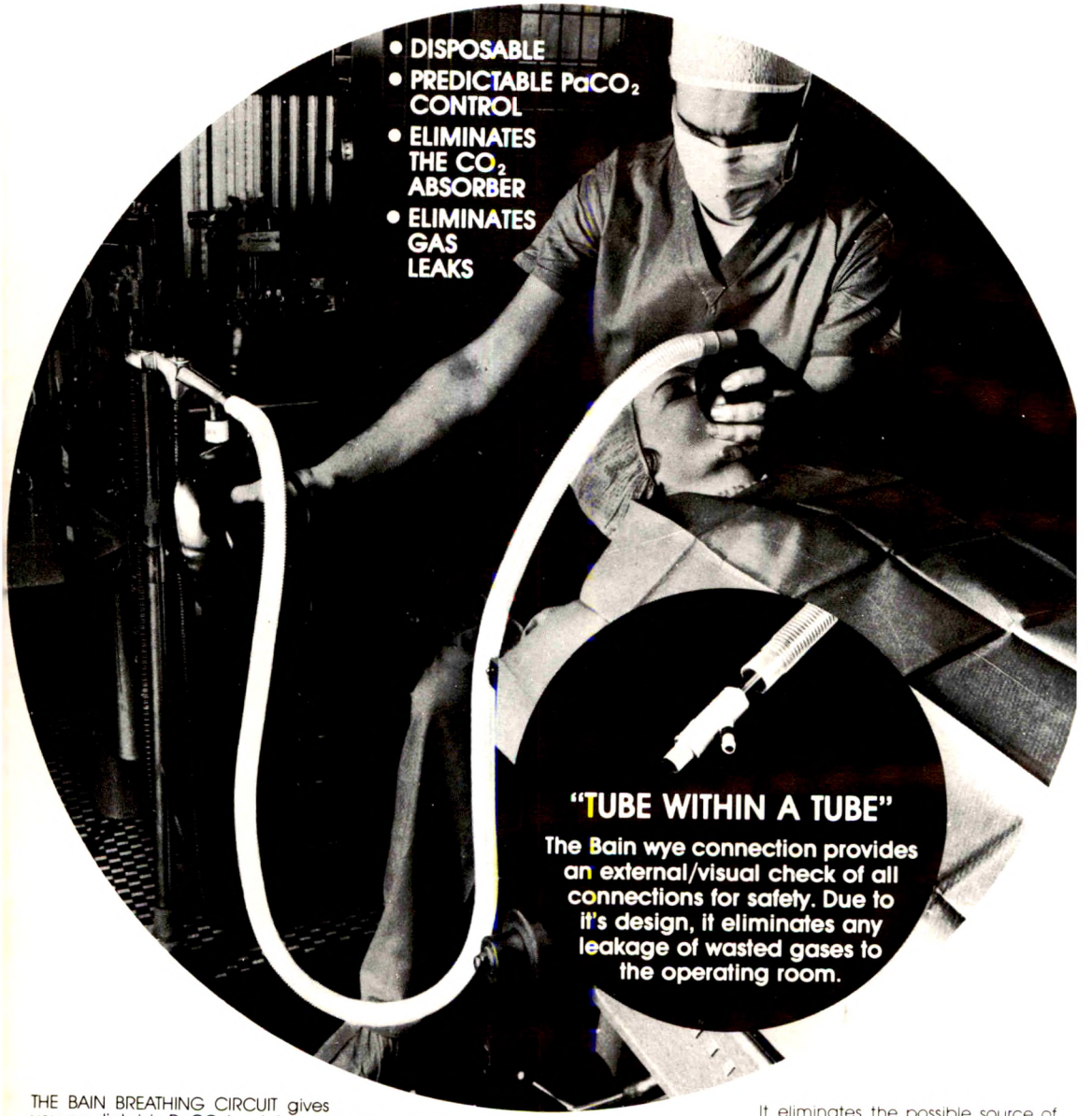
MANAGEMENT OF ADVERSE REACTIONS: Apnea or prolonged muscle paralysis should be treated with controlled respiration. The use of neostigmine to reverse nondepolarization block is a medical decision which must be made on the basis of individual clinical pharmacology and the experience and judgment of the clinician. When neostigmine is used, atropine should also be administered.

HOW SUPPLIED: Injection, multi-dose vials, 20 mg/cc, 10 cc, boxes of 12 vials. Flo-Pack® Sterile Powder 500 mg and 1000 mg, boxes of 12. Complete literature available on request from Professional Services Dept. PML.

Wellcome

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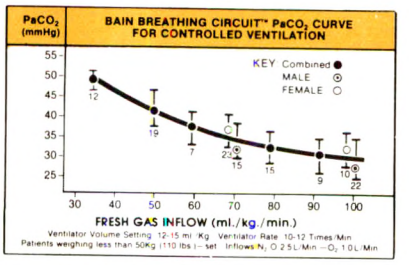
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THE BAIN BREATHING CIRCUIT gives you predictable $PaCO_2$ levels based on clinical studies* using blood gas determination data.

It is a highly streamlined system that offers greater convenience and patient safety.

It creates a continuous flow system that requires no soda-lime absorber —eliminates all one-way valves from the system. The system is long enough to provide flexibility for the surgeon, particularly in procedures on the head, face and neck. Provides **natural** humidity control, thus higher humidity than the absorber method.

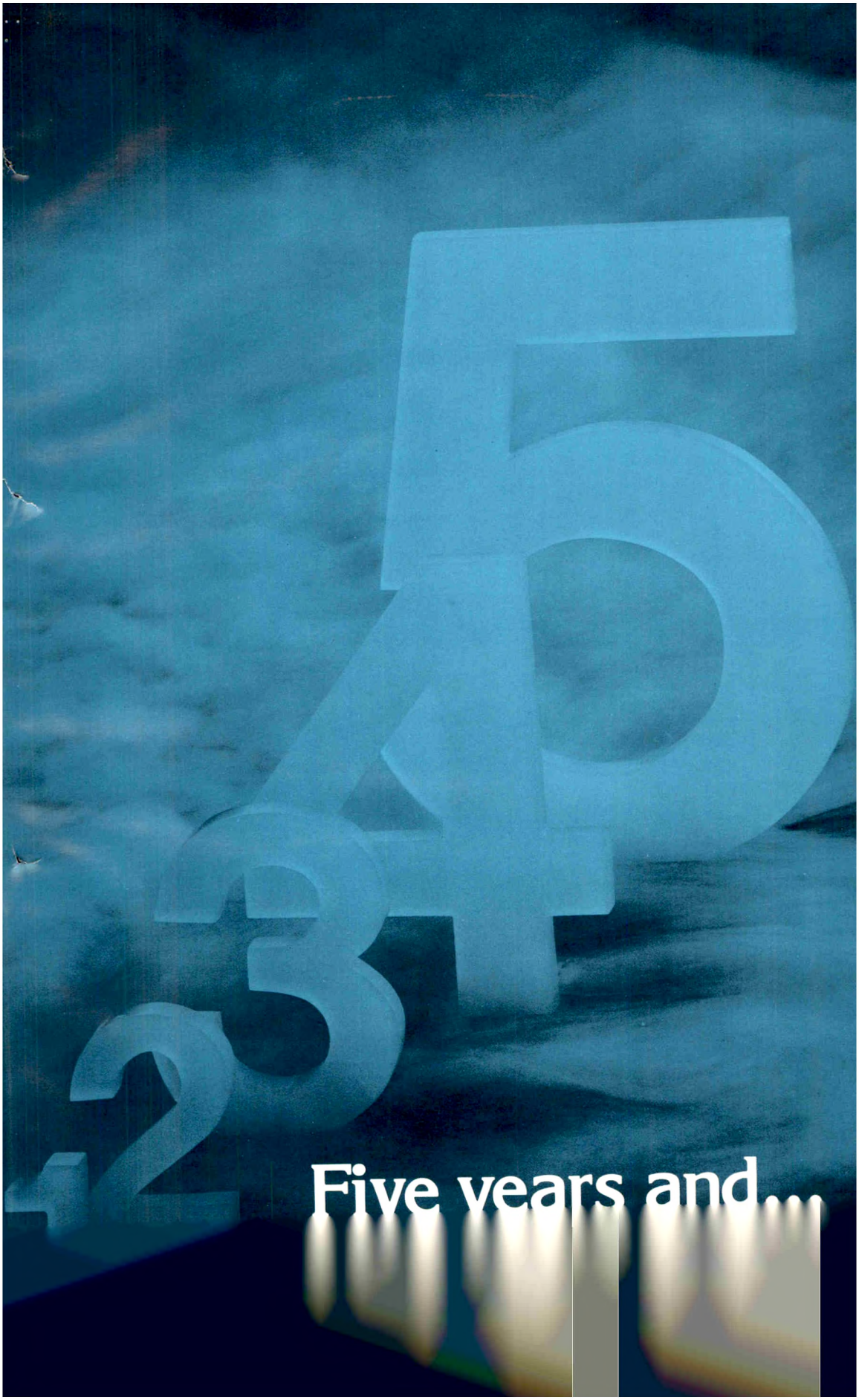


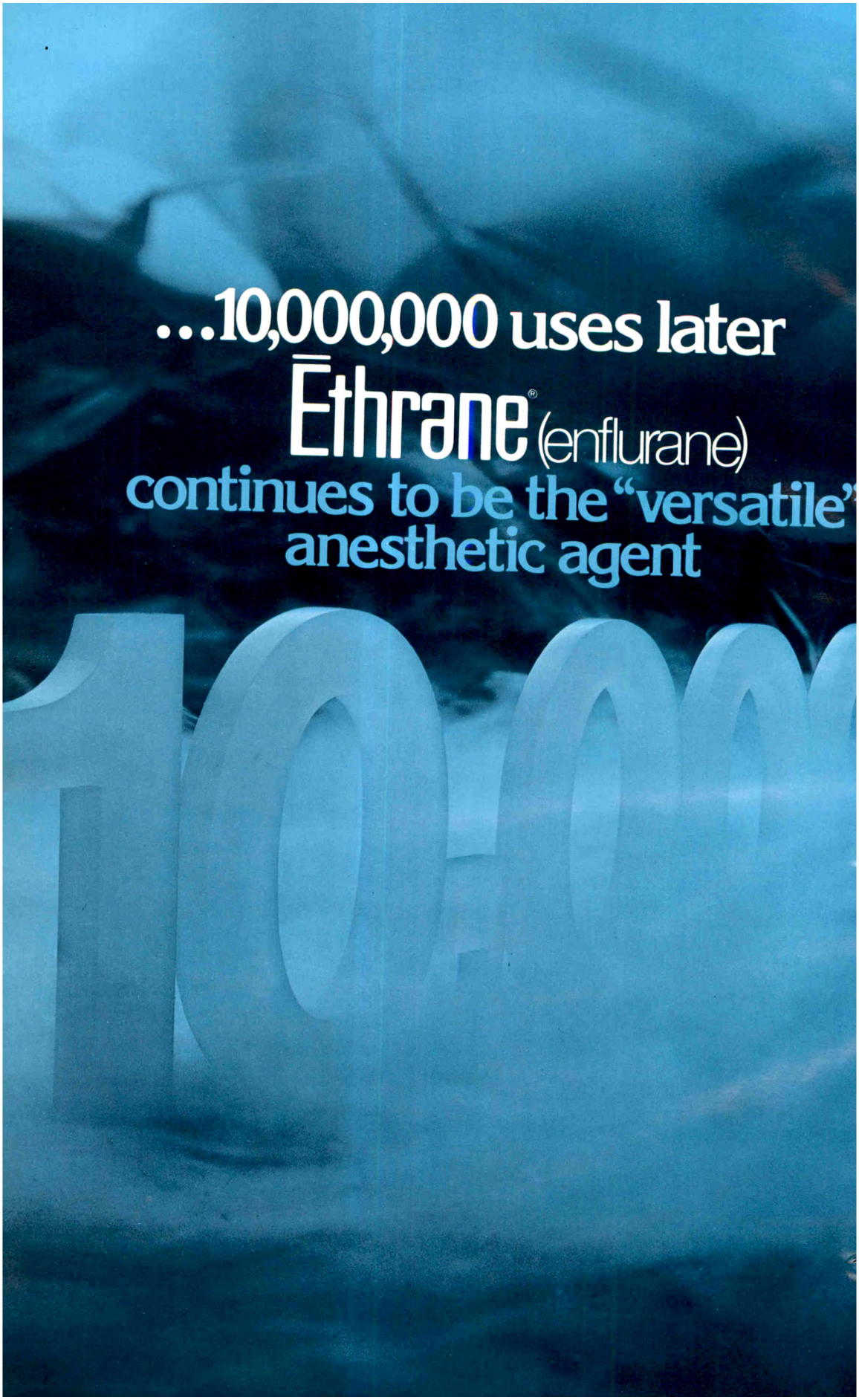
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It eliminates the possible source of cross-contamination. It is versatile—can be used with adults, as well as children and with virtually any gas machine and anesthetic gases.

The Bain Breathing Circuit—disposable, predictable, convenient, efficient—the ultimate in greater patient safety.

*"Prediction of Arterial Carbon Dioxide Tension During Controlled Ventilation with a Modified Mapleson 'D' System," by J. A. Bain and W. E. Spoerel. CANADIAN ANAESTH. SOC. JOURNAL. Volume 22, No. 1, Jan. 1975.


Five years and...


...10,000,000 uses later
Ethrane® (enflurane)
continues to be the "versatile"
anesthetic agent

CP 24,574

Now with documented epinephrine compatibility

ETHRANE® (enflurane) does not contraindicate the use of exogenous epinephrine*[1-4]—so important during local hemostasis (with or without concomitantly used lidocaine).[1-4] Ventricular arrhythmias are less likely to occur following concomitant use of ETHRANE and subcutaneously administered epinephrine, than with a halothane/epinephrine combination.[1,2,5] Of course, all customary precautions in the use of vasoconstrictor substances should be observed.

ETHRANE has also been used successfully in pheochromocytoma resection.[6-8] None of these patients displayed ventricular extrasystoles despite increased blood pressures and tachycardia.

Besides this compatibility with epinephrine, ETHRANE has demonstrated the following advantages over many other anesthetic agents in over 10,000,000 uses to date: rapid smooth induction, prompt recovery, maintenance of stable cardiac rhythm, excellent muscle relaxation, and few postanesthetic side effects.

ETHRANE–the anesthetic agent that continues to be versatile...10,000,000 uses later

WARNING: Motor activity exemplified by movement of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia. For additional warnings, contraindications, and precautions, see following page.

*Please see following page for product information.

References:

1. Johnston, R.R., et al.: A comparative interaction of epinephrine with enflurane, isoflurane, and halothane in man: Epinephrine induced PVC's and anesthesia. Anesth & Analg **55**:709-712, 1976.
2. Reisner, L.S., Lippmann, M.: Ventricular arrhythmias after epinephrine injection in enflurane and in halothane anesthesia. Anesth & Analg **54**:468-470, 1975.
3. Lippmann, M., Reisner, L.S.: Epinephrine injection with enflurane anesthesia: Incidence of cardiac arrhythmias. Anesth & Analg **53**:868-889, 1974.
4. Konchigeri, H.N., et al.: Effect of epinephrine during enflurane anesthesia. Anesth & Analg **53**:894-897, 1974.
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6. Kreul, J.F., et al.: Hemodynamic and catecholamine studies during pheochromocytoma resection under enflurane anesthesia. Anesthesiology **44**:265-268, 1976.
7. Ortiz, F.T., Diaz, P.M.: Use of enflurane for pheochromocytoma removal. Anesthesiology **42**:495-497, 1975.
8. Kopriva, C.J., Eltringham, R.: The use of enflurane during resection of a pheochromocytoma. Anesthesiology **41**:399-400, 1974.

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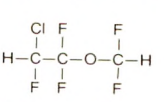
AIRCO®

Ethrane®
(enflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription.

DESCRIPTION

ETHRANE (enflurane) is a nonflammable inhalation anesthetic agent. It is 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether, molecular weight 184.5, and its structural formula is:



The boiling point is 56.5°C at 760 mm Hg, and the vapor pressure (mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C. Vapor pressures can be calculated using the equation:

$\log_{10} P = A + B/T$ $A = 7.967$

$B = -1678.4$

$T = °C + 273.16$ (Kelvin)

The specific gravity (25°/25°C) is 1.517. The refractive index at 20° is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C. The M.A.C. (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70% nitrous oxide and oxygen, and 1.17 in 30% nitrous oxide and oxygen.

ETHRANE is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No chemical stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary to maintain stability even in the presence of ultraviolet light. ETHRANE is stable to strong base and does not decompose in contact with soda lime and does not attack aluminum, tin, brass, iron or copper. The partition coefficients of ETHRANE at 25° C are 74 in conductive rubber and 120 in polyvinyl chloride.

ACTIONS

ETHRANE (enflurane) is an inhalation anesthetic. Induction and recovery from anesthesia with ETHRANE are rapid. ETHRANE has a mild, sweet odor. There is mild stimulus to salivation or tracheobronchial secretions when ETHRANE is used alone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia changes rapidly with ETHRANE. ETHRANE reduces ventilation as depth of anesthesia increases. High pCO_2 levels can be obtained at deeper levels of anesthesia if ventilation is not supported. ETHRANE provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during ETHRANE anesthesia. ETHRANE anesthesia has been used in excision of pheochromocytoma in man without ventricular arrhythmias. On the basis of studies in patients anesthetized with ETHRANE and injected with epinephrine containing solutions to achieve hemostasis, up to 10 ml of 1:100,000 or 1:200,000 epinephrine containing solution may be injected subcutaneously at a rate of not more than 10 ml per minute and no more than 30 ml per hour. All customary precautions in the use of vasoconstrictor substances should be observed.

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with ETHRANE. THE NONDEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED. In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height. Neostigmine does not reverse the direct effect of ETHRANE.

Biotransformation of ETHRANE in man results in low levels of serum fluoride ions averaging 15 mM/L. These levels are well below the 50 mM/L threshold level which can produce minimal renal damage in normal subjects; however, it is possible that these levels could result in damage in patients with severely impaired renal function or those undergoing renal transplantation. Depression of lymphocyte transformation does not follow prolonged ETHRANE anesthesia in man in the absence of surgery. Thus ETHRANE does not depress this aspect of the immune response.

INDICATIONS

ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Seizure disorders (see WARNINGS).

Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics.

WARNINGS

Increasing depth of anesthesia with ETHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentration usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental function testing does not reveal any impairment of performance following prolonged ETHRANE anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

The action of nondepolarizing relaxants is augmented by ETHRANE. Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from myoneural blockade will be longer in the presence of ETHRANE than for other commonly used anesthetics.

Usage in Pregnancy: Safety in pregnancy has not been established. Reproduction studies have been performed in rats and rabbits, and there is no evidence of harm to the animal fetus. The relevance of the studies to the human is not known. Since there is no adequate experience in pregnant women who have received the drug, safety in pregnancy has not been established.

PRECAUTIONS

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. ETHRANE (enflurane) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug. As with other general anesthetics and some muscle relaxants, hyperpyrexia has been observed with the use of ETHRANE.

ADVERSE REACTIONS

1. Motor activity exemplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia, or light levels with hypocapnia.
2. Hypotension and respiratory depression have been reported.
3. Arrhythmias, shivering, nausea, and vomiting have been reported.
4. Elevation of the white blood count has been observed.

DOSAGE AND ADMINISTRATION

The concentration of ETHRANE (enflurane) being delivered during anesthesia from a vaporizer should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for ETHRANE;
b) vaporizers from which delivered flows can easily and readily be calculated.

Nothing is present in the agent to alter calibration or affect the operation characteristics of the vaporizer.

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ETHRANE and the heart rate remains constant. The use of anticholinergic drugs is a matter of choice.

Induction: Induction may be achieved using ETHRANE alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the ETHRANE mixture. In general, inspired concentrations of 3.5-4.5% ETHRANE produce surgical anesthesia in 7-10 minutes.

Maintenance: Surgical levels of anesthesia may be obtained with 1.5-3% ETHRANE. Maintenance concentrations should not exceed 3%. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of ETHRANE concentration in the absence of other complicating problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Overdosage: In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration; establish that the airway is clear and initiate assisted or controlled ventilation with pure oxygen as circumstances dictate.

PACKAGING

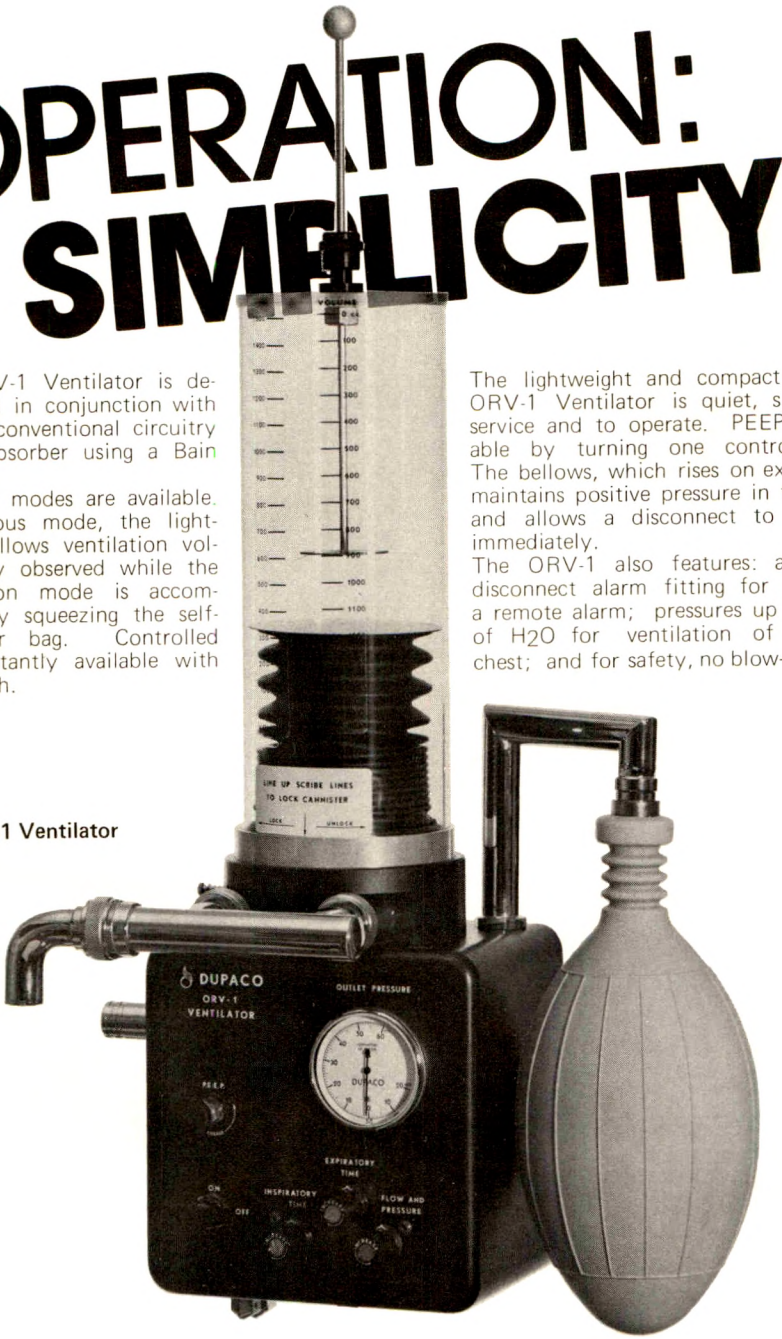
ETHRANE (enflurane) is packaged in 125 and 250 ml amber colored bottles.

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AIRCO®

OPERATION: SIMPLICITY

The Dupaco ORV-1 Ventilator is designed to be used in conjunction with an absorber and conventional circuitry or without an absorber using a Bain type circuit.
Three operational modes are available. In the spontaneous mode, the lightweight bellows allows ventilation volume to be easily observed while the assisted ventilation mode is accomplished by simply squeezing the self-inflating reservoir bag. Controlled ventilation is instantly available with the turn of a switch.

The lightweight and compact Dupaco ORV-1 Ventilator is quiet, simple to service and to operate. PEEP is available by turning one control knob. The bellows, which rises on exhalation, maintains positive pressure in the lungs and allows a disconnect to be seen immediately.
The ORV-1 also features: a built-in disconnect alarm fitting for use with a remote alarm; pressures up to 80cm of H_2O for ventilation of the stiff chest; and for safety, no blow-off valve.

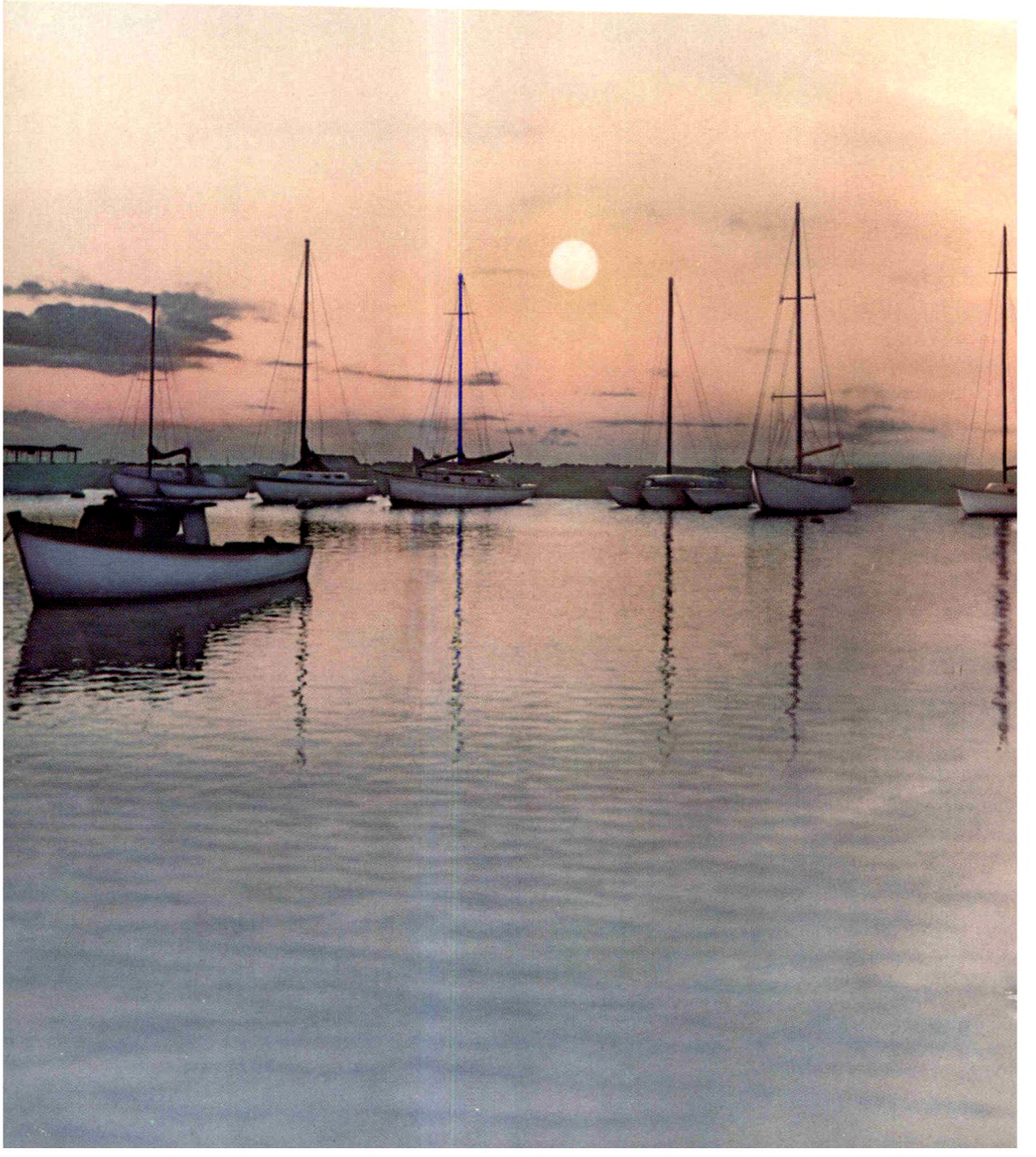


The Dupaco ORV-1 Ventilator

DUPACO

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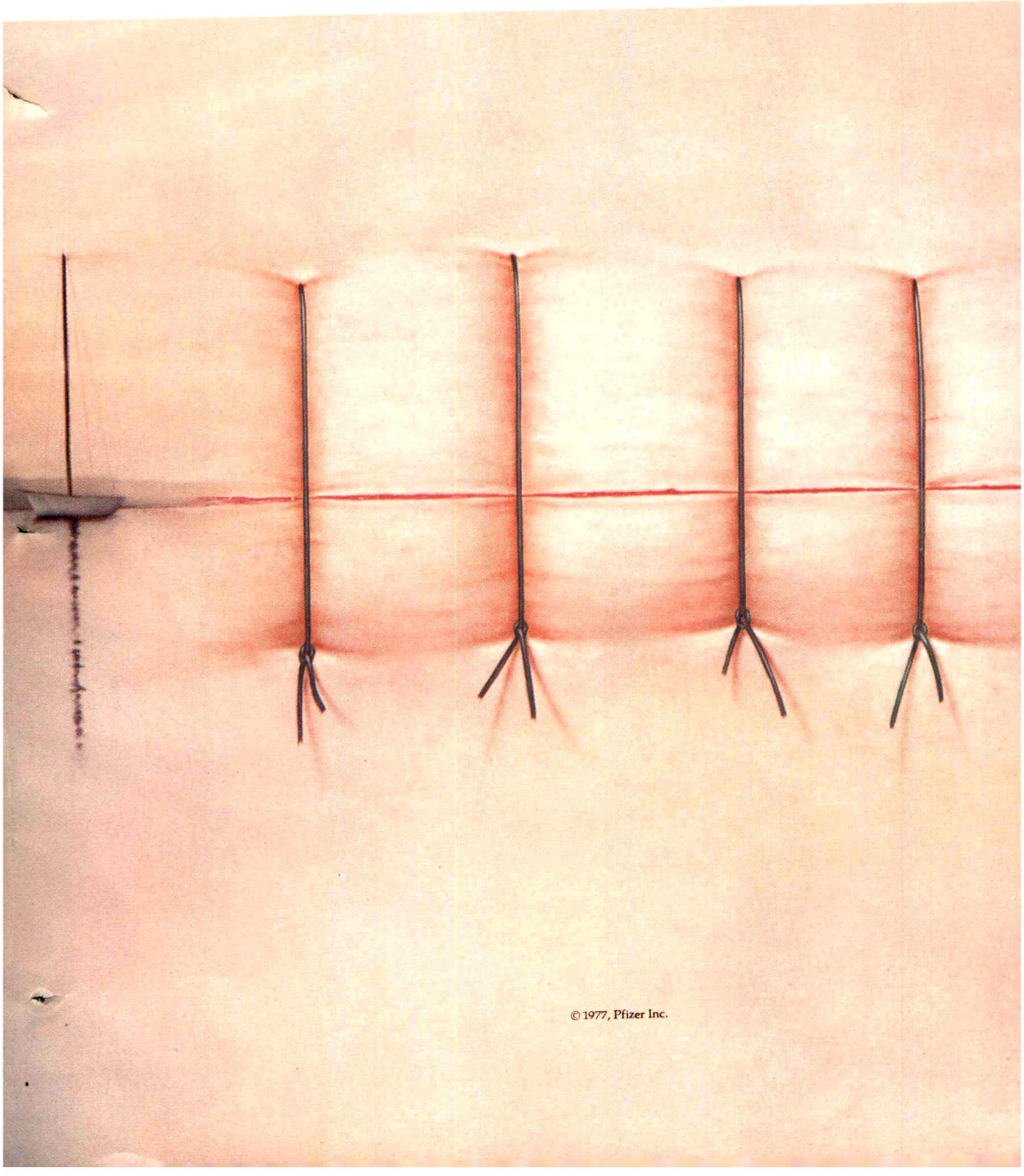


Vistaril® I.M.
(hydroxyzine HCl)

—allays anxiety
—reduces narcotic requirements
—and controls emesis

o surgery

Please see Brief Summary on following page for contraindications, precautions and adverse reactions.



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Vistaril® I.M.
(hydroxyzine HCl)
100 mg/2 ml—50 mg/ml and
25 mg/ml Vials and Isojects®

preoperatively and postoperatively

- **allays presurgical anxiety...allays the anxiety that may heighten the perception of postoperative pain**
- **may enhance the effects of analgesics and reduce narcotic requirements**
- **controls postoperative emesis**
- **vital signs are seldom impaired (Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.)**

BRIEF SUMMARY
VISTARIL® (hydroxyzine hydrochloride)
Intramuscular Solution/For Intramuscular Use Only
Contraindications: Hypersensitivity to hydroxyzine. The solution for intramuscular use *must not* be injected subcutaneously, intra-arterially, or intravenously.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate. Until adequate data are available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.
Precautions: HYDROXYZINE MAY POTENTIATE THE ACTION OF CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS AND BARBITURATES. In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. Inadvertent subcutaneous injection may result in significant tissue damage. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscle of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in order to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults and older children, and only with caution to avoid radial nerve injury. Injections should not be made in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid intravascular injection.
Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.
Supply: Vistaril (hydroxyzine HCl) Intramuscular Solution: 25 mg/ml—10 ml vial; 50 mg/ml—2 ml and 10 ml vial; Isoject® 25 mg/ml and 50 mg/ml, 1 ml fill; 100 mg/2 ml, 2 ml fill.
Military Depot: NSN 6505-00-052-1367 (50 mg/ml, 10 ml vial)
VA Depot: NSN 6505-00-052-1367B (50 mg/ml, 10 ml vial)
More detailed professional information available on request.

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International Anesthesia Research Society

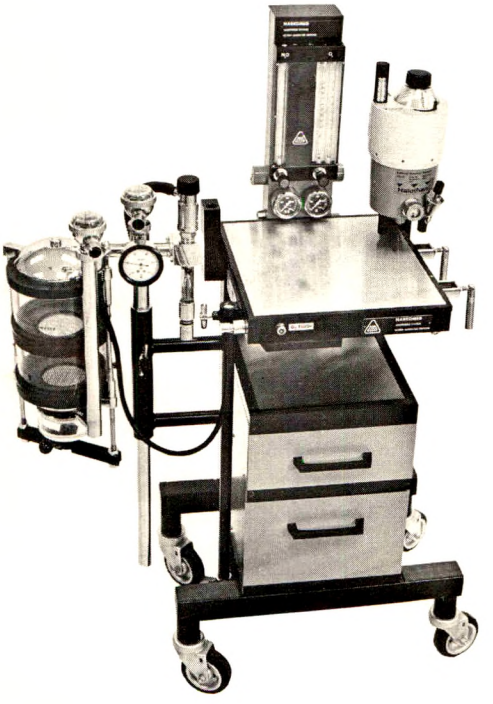
52nd Congress

March 19-23, 1978

The San Francisco Hilton

San Francisco, California

NARKOMED COMPACT



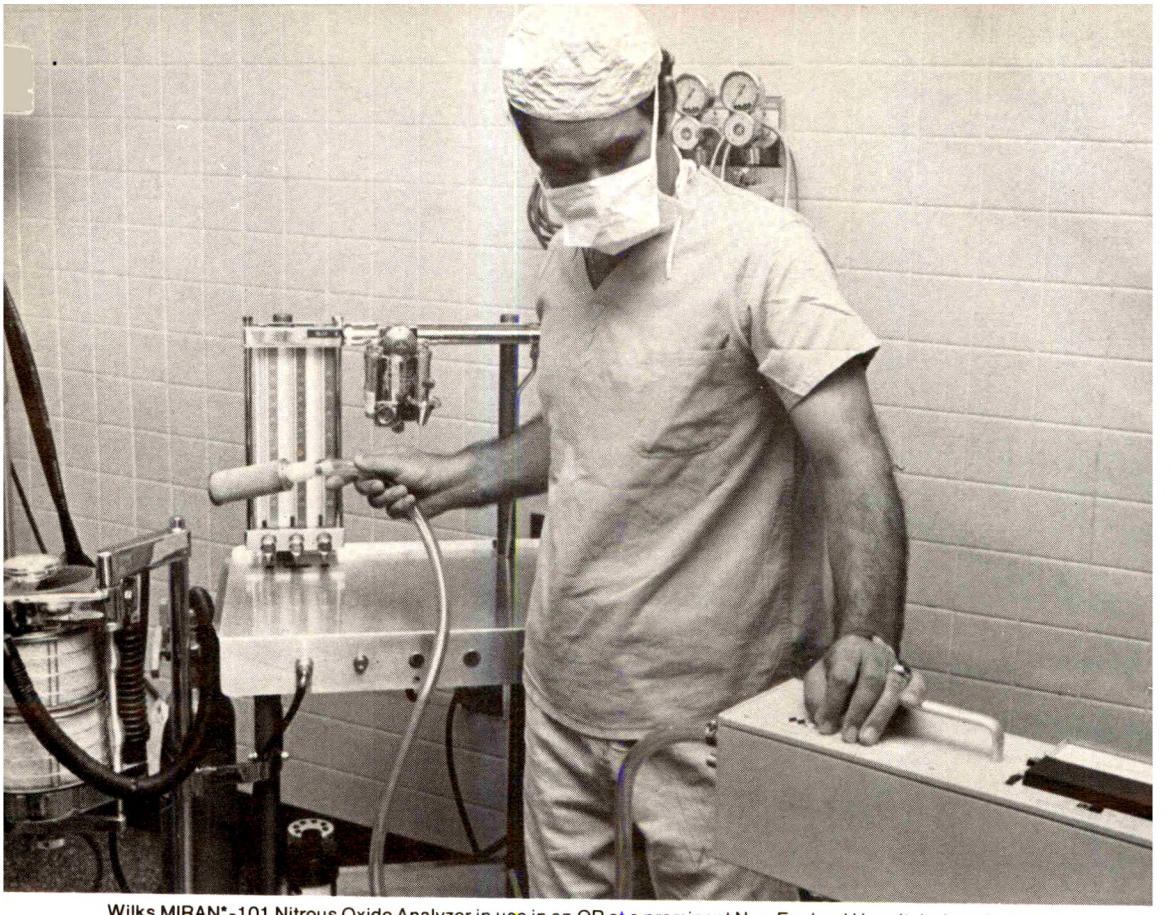
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North American Drager is pleased to announce a new member to our Narkomed family of Anesthesia Machines "The Narkomed Compact" — contemporary in design and styling utilizing many of our standard Narkomed components assembled on a smaller frame for use where floor space is at a premium. A refreshing new dimension in Anesthesia Machine design and styling — "The Narkomed Compact."

Write for Complete Details

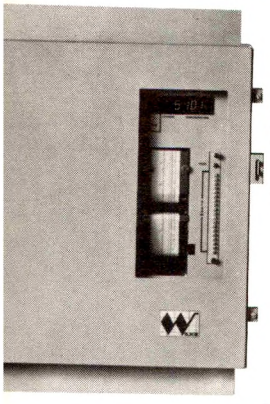
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Wilks MIRAN*-101 Nitrous Oxide Analyzer in use in an OR at a prominent New England Hospital where it checks for leaks in delivery systems and monitors background levels of anesthetic gas.

Protect your OR people from pathological effects of low-level anesthetic gas.



MIRAN-201 15-Point Continuous Air Monitor. Monitors locations up to 400 feet distant, records concentration versus time, toxic level alarms.



MIRAN-1A General-Purpose Gas Analyzer. Can be used to measure all organic vapors in the ppm range.

Substantial evidence exists that long-term exposure to anesthetic g in the OR atmosphere can have significant pathological effects on OR personnel. The National Institute of Occupational Safety and Health (NIOSH) has recommended that background levels of nitrous oxide be kept below 25 ppm and that regular checks be made in the OR and adjacent areas. The infrared gas analyzer is a recommended analytical method.

Wilks supplies several different instruments for Hospital use. They include: MIRAN-101 — a portable, specific analyzer for N_2C MIRAN-1A — a general-purpose analyzer capable of measuring al anesthetic gases; MIRAN-201 — a multi-station continuous monit which provides continuous records of gas leaks at up to 15 remote locations with adjustable alarms.

The 201 has the data-handling capacity to meet OSHA requirements for calculating long-term exposure for OR personnel. The two portable instruments (1A, 101) are ideal for leak detection in anesthetic machines and gas delivery systems — sometimes saving their cost in reduced gas usage — and checking scavenging system performance as well as background gas concentration monitoring.

Call or write us for complete information on gas analyzers for OR use. Foxboro/Wilks, Inc., PO Box 449, S. Norwalk, CT 06856. (203) 853-1616.

*Registered trademark of Foxboro/Wilks, Inc.

WILKS
Foxboro/Wilks, Inc.

International Anesthesia Research Society

52nd Congress

March 19 - 23, 1978 - San Francisco, Hilton Hotel

MEETING SCHEDULE

Registration: Sunday, March 19 — 1 to 7 p.m.

Scientific Program: Monday, March 20 — Thursday, March 23 — 8:30 a.m. to 5 p.m. daily

Throughout the entire 4-day scientific meeting, concurrent sessions will be held—except for the Baxter/Travenol and Becton, Dickinson Lectures which will be given at single sessions on Monday and Tuesday afternoons, respectively. The entire Thursday program will be devoted to Review Courses. A total of 64 scientific papers and 12 review courses will be offered in addition to the aforementioned Lectures.

PRELIMINARY PROGRAM

MEETING REGISTRATION AND HOTEL RESERVATION CARDS

These are available from the Cleveland office of the I.A.R.S.

FEES	Paid by March 15	Paid at Meeting
IARS Members	$35.00	$ 50.00
IARS Educational Members	NO FEE	NO FEE
Non-IARS Members	$75.00	$100.00

SCIENTIFIC AND TECHNICAL EXHIBITS

Individuals or institutions wishing to present scientific exhibits should request application forms from Cleveland business office. Commercial firms desiring exhibit space should contact Charles B. Slack, Inc., 6900 Grove Rd., Thorofare, New Jersey 08086.

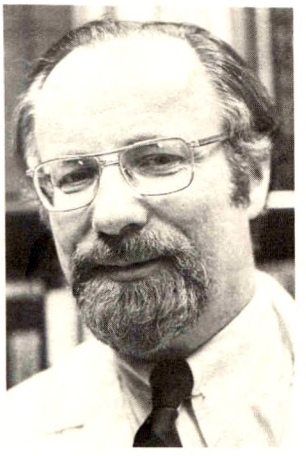
CONTINUING MEDICAL EDUCATION CREDIT

As an organization accredited for continuing medical education, the International Anesthesia Research Society certifies that the continuing medical education activities designated Category 1 meet the criteria for Category 1 on an hour-for-hour basis for the Physicians Recognition Award of the American Medical Association. (Note: An individual who takes full advantage of the scientific program can accumulate a maximum of 24 credit hours in Category 1, or 6 hours for each full day of attendance.)

PLAN TO  BE ABOARD

IARS 52nd Congress Distinguished Lecturers

Thirteenth Annual Becton, Dickinson and Company Oscar Schwidetzky Memorial Lecture



Monday, March 20 - 1:30 p.m.

"New Concepts of Shock and Its Management"

Max Harry Weil, MD, PhD
Director and Clinical Professor
of Medicine and Biomedical Engineering
University of Southern California
Los Angeles, California

Sixteenth Annual Baxter/Travenol Lecture

Tuesday, March 21 - 1:30 p.m.

"Pediatric Anesthesia in Perspective"



Robert M. Smith, MD
Director of Anesthesia
Children's Hospital Medical Center
Clinical Professor of Anesthesia
Harvard Medical School
Boston Massachusetts

RO 21-3981 for Intravenous Surgical Premedication and Induction of Anesthesia

JAMES T. CONNER, MD*
RONALD L. KATZ, MD†
RICHARD R. PAGANO, MD‡
CHARLES W. GRAHAM, MD, PhD‡
Los Angeles, California§

RO 21-3981, a new water soluble benzodiazepine, was studied in 24 patients both as an intravenous premedicant and to induce anesthesia. The premedicant dose of 5 mg produced lack of recall and marked sedation within 1 to 2 minutes after injection and persisted for at least 32 minutes. Subsequent induction of anesthesia required an additional 5 to 25 mg of RO 21-3981. However, anesthesia was not induced in 1 patient with 25 mg and was accomplished only with inhalation anesthesia. Loss of lid reflex was unreliable as a sign of induction for patients in whom tracheal intubation was planned. Although decreases in blood pressure of 10 to 30 mm Hg were noted after administration of RO 21-3981, systolic pressure was not recorded below 90 mm Hg. RO 21-3981, because of its amnesic, sedative, and anxiolytic properties, appears to be an excellent premedicant although the 5 mg dose studied was probably larger than necessary. For induction of anesthesia, RO 21-3981 may be an effective alternative to thiopental.

Key Words — PREMEDICATION, RO 21-3981. ANESTHETIC TECHNICS, induction.

RO 21-3981, 8-chloro-6-(2 fluorophenyl)-1-methyl-4H-imidazo(-)[1,5-a] [1,4)]) benzodiazepine maleate (see figure), is a water soluble benzodiazepine which produces sleep in volunteers when given intravenously in doses up to 10 mg (M. Ravin, personal communication). It has been proposed that RO 21-3981 may be useful intravenously to induce general anesthesia. In this study, we used the drug both as an intravenous premedicant and for induction of anesthesia to determine its clinical usefulness. For the premedication study, sedation, relief of anxiety, lack of recall, and patient acceptance were evaluated.

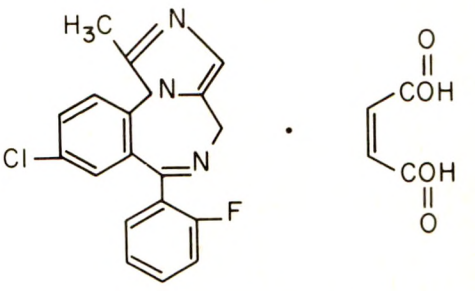


FIGURE. Molecular structure of RO 21-3981

METHOD

Twenty-four patients, ASA Class I, between the ages of 19 and 58 participated in the study. They were chosen from the elective schedule of plastic surgery, orthopedics, gynecology, general surgery, and urology. Informed consent was obtained from all patients.‖ No patient received any other preoperative sedative or analgesic. All patients

‖This study was approved by the UCLA Human Subject Protection Committee.

*Assistant Professor, Department of Anesthesiology
†Professor and Chairman, Department of Anesthesiology
‡Resident, Anesthesiology
§Department of Anesthesiology, UCLA School of Medicine, Los Angeles, California 90024

This study is supported by Hoffmann-La Roche, Inc., the UCLA Foundation, and Medrec, Inc.
Accepted for publication: May 13, 1977

received inhalation anesthesia with halothane or enflurane plus N_2O and O_2.

Patients were brought to a preoperative holding area approximately 1 hour prior to surgery. An intravenous infusion was started and RO 21-3981 5 mg was administered as an intravenous premedicant during 1 minute. A trained nurse observer recorded patient responses throughout the preoperative period. Prior to being medicated, the patient was asked to evaluate his anxiety as none, mild, moderate, or severe. Vital signs were checked before and after injection and observations were made for signs and symptoms of possible side effects or sensitivity throughout the study period. After receiving the drug, patients were asked how they felt and if they had any subjective sensations or complaints at the times indicated below.

Recall was tested by showing the patient a different "memory card" (large cardboard pictures of familiar objects or persons) 1, 2, 4, 8, 16, and 32 minutes after injection. The patient was asked to identify each and was told that he would be asked to recognize the pictures the day following surgery. The order of the card presentation was randomized.

Four minutes after RO 21-3981 administration, the nurse observer, without informing the patient, scored the patient's level of sedation as 1+, 2+, 3+, or 4+ (improved over his unpremedicated state); 1–, 2–, 3–, or 4– (worsened); or 0 (unchanged). The patient was then asked to score his anxiety level as compared to his unpremedicated state on a similar scale. The patient was asked if the overall effect of the drug was pleasant, unpleasant, or neutral. The patient was similarly re-evaluated 8, 16, and 32 minutes after injection.

It should be pointed out that relief of anxiety and sedation are not synonymous. When a patient experiences relief of anxiety, he may or may not appear sedated to an observer. Conversely, a patient may appear to be sedated but still be anxious. Anxiety is a subjective response by the patient while sedation is an observed response.

The physician who administered the drug accompanied the patient to the operating room, where additional RO 21-3981 was slowly administered intravenously for induction of general anesthesia, using the loss of the lid reflex as an indicator of adequate induction. At this time, patients who were to have endotracheal tubes inserted were given succinylcholine, intubated, and then given an appropriate percentage of N_2O and enflurane or halothane for maintenance of anesthesia. Patients who were not intubated received inhalational anesthesia by mask after loss of lid reflex. Vital signs were checked every 1 to 5 minutes during induction and throughout subsequent anesthesia and surgery. In the recovery room, the time of the patient's response to command was noted as was the occurrence of agitation, nausea, and vomiting.

Postoperative interviews were conducted 24 hours after surgery by the nurse observer. Each patient was asked to rate the drug as both a premedicant and induction agent, using his own subjective criteria as poor (0), fair (1+), good (2+), or excellent (3+). The patient was also asked if he would like the drug again for another operation. Recall was evaluated by asking the patient if he remembered the intravenous infusion being started and the operating room. Then the patient was shown a large composite of 8 pictures which included the 6 memory cards and was asked if he could remember being shown any of the pictures. The patient was not told how many pictures he had been shown or if his recall was correct. The site of injection was checked for clinical signs of thrombophlebitis.

The anesthesia record, recovery room records, and postoperative notes were examined for surgical or anesthetic complications which might be related to RO 21-3981. Statistical analysis of data consisted of computation of mean raw scores and standard deviations.

RESULTS

Evaluation as a Premedicant

Patient's Evaluation of Anxiety (Table 1)—The relief of anxiety was high at all time intervals. The lowest mean raw score was 3.1 out of a possible 4.0.

Nurse's Evaluation of Sedation (Table 1)—The sedation scores were also high at all time intervals, and mean raw scores for sedation were similar to the anxiety relief scores.

Effect on Recall (Table 2)—There was a high incidence of failure to recall. Ninety-six percent of the patients could not recall the 2-minute memory card. At 32 minutes, 69 percent of the patients could not recall

TABLE 1
RO 21-3981 (5 Mg) IV as Premedication

Relief of anxiety score by patient	(Mean) (SD)
4 minutes	3.50 ± 0.67
8 minutes	3.55 ± 0.65
16 minutes	3.39 ± 0.89
32 minutes	3.11 ± 1.26
Patient sedation scored by nurse observer	(Mean) (SD)
4 minutes	3.18 ± 0.81
8 minutes	3.50 ± 0.59
16 minutes	3.60 ± 0.59
32 minutes	3.03 ± 0.99
Patient acceptance (0-3) at 24 hours	
Excellent (3+)	19 (79%)
Good (2+)	5 (21%)
Fair (1+)	0 (0%)
Poor (0)	0 (0%)
Patient evaluation at 4 minutes	
Pleasant	22 (92%)
Unpleasant	1 (4%)
No opinion	1 (4%)
Patient preference to taking drug again	
Yes	24 (100%)
No	0 (0%)
Mean age	36.2 ± 11.1
Mean weight (kg)	74.7 ± 14.3
Mean height (cm)	170.0 ± 9.8
Sex (male/female)	18/6

the memory card. All patients remembered the initial injection of the drug, indicating no retrograde amnesia. Failure to recall entering the operating room (which occurred at a mean time of 43 minutes) was 57 percent. Failure to recall the recovery room was 71 percent.

Patient Acceptance (Table 1)—Patients readily accepted the medication. At 4 minutes after injection, 92 percent of the patients said it gave them a pleasant feeling. The next day, all said they would accept the drug if they had another operation. The reasons given for their liking the drug were relief of anxiety and lack of recall.

Preoperative Side Effects (Table 3)—Dizziness or lightheadedness was a complaint of almost half of the patients. Other subjective patient complaints were unusual. One patient, a 100-kg male, lost consciousness 2 to 3 minutes after injection and developed soft tissue airway obstruction which required a nasal airway. In 17 of the 24 patients, systolic pressure decreased following premedication. The average decrease in these 17 patients was 18 mm Hg. The largest decrease, 30 mm Hg, occurred in 2 patients. The heart rate was usually not altered. However, an athletic patient had a decrease from 60 to 46 beats per minute after injection of RO 21-3981. His pulse rate increased from 46 to 60 after 0.6 mg of atropine.

Recovery Room—Eighteen of the 24 patients were responsive to oral command upon arrival in the recovery room. Of the 6 patients still asleep, all but 1 were responsive within 20 minutes. The exception continued sleeping for 85 minutes in the recovery room. No patient was agitated. One patient complained of nausea.

Evaluation for Induction of Anesthesia

Loss of lid reflex, our index that general anesthesia had been induced, usually required from 5 to 20 mg of RO 21-3981 injected over 1 to 2 minutes, in addition to the 5 mg premedicant dose. One patient (male, 39 years, 65 kg) did not lose con-

TABLE 2
RO 21-3981 (5 Mg) IV Premedication: Failure To Recall

	Percentage		Percentage
Memory card 1 minute	91	Memory card 32 minutes	69
Memory card 2 minutes	96	Operating room entry (Mean time—43 minutes)	57
Memory card 4 minutes	78	Recovery room	71
Memory card 8 minutes	87	Injection of RO 21-3981 (in preoperative room)	0
Memory card 16 minutes	75		

TABLE 3
RO 21-3981 (5 Mg) IV Premedication
Side Effects: Preoperative

	Percentage		Percentage
Dizziness (lightheadedness)	46	Pain on injection	
Blurred vision	8	None	92
Bad taste	4	Mild	8
Hiccoughs	4	Severe	0
Nausea	0	Thrombophlebitis (24 hours)	0
Vomiting	0		

Systolic blood pressure:	(Mean) (SD)	Heart rate:	(Mean) (SD)
Prior to injection	116 mm Hg ± 13	Prior to injection	71 ± 9
After injection	104 mm Hg ± 12	After injection	74 ± 12

sciousness after 25 mg of RO 21-3981. Induction was completed with N_2O and enflurane. The patient most sensitive to RO 21-3981 (male, 22 years, 100 kg) became unresponsive after 5 mg.

Twelve of the 24 patients were given succinylcholine to facilitate tracheal intubation. Many of the patients who had lost their lid reflexes made what appeared to be purposeful arm and hand movements at the start of muscle fasciculation. Two patients who were given a larger dose of RO 21-3981 (20 mg in 1 injection) did not demonstrate these purposeful movements.

None of the patients had any undesirable intraoperative or postoperative side effects which were thought to be related to RO 21-3981. There were no alarming changes in vital signs, although decreases in blood pressure of 10 to 20 mm Hg after induction and prior to intubation were not uncommon. Brief apnea of 10 to 15 seconds was noted in some patients after induction. There was no indication of drug interaction between RO 21-3981 and any of the drugs used during anesthesia.

DISCUSSION

Diazepam and lorazepam, both benzodiazepines, have proven to be excellent intravenous premedicants. We therefore decided to test RO 21-3981, a new benzodiazepine, as a surgical premedicant. A 5-mg dose was chosen arbitrarily for premedication. In retrospect, this is probably a larger dose than necessary for most patients although there is a large patient variation in response. Scores of sedation, relief of anxiety, and lack of recall were high in comparison to a number of intravenous premedicants in a series of studies done by us with the same method; these drugs include intravenous narcotics, promethazine, scopolamine, hydroxyzine, lorazepam, and diazepam.[1-5] Several patients were so sedated after 5 mg of RO 21-3981 that they could not be aroused to identify the memory cards, and 1 patient had soft tissue airway obstruction following this dosage. The frequency of lack of recall was the highest we have seen for any intravenous surgical premedicant, including diazepam[2] 20 mg, lorazepam[1] 4 mg, or lorazepam 4 mg plus scopolamine 0.4 (unpublished data). The effects of RO 21-3981 were only slightly diminished 32 minutes after injection, although the duration of effect may be less if lower dosages are administered. Although we found a decrease in systolic pressure in a majority of the patients, none of these changes was alarming since in no instance did systolic pressure decrease below 90 mm Hg. Side effects were minimal, with dizziness being the most frequent complaint. Undiluted injections did not cause pain, in marked contrast to past observations with diazepam, and no clinical evidence of thrombophlebitis was seen the day after surgery. Patient acceptance was high, and all patients stated that they would take the drug again, primarily because of the lack of recall and relief of anxiety.

Thiopental is the most frequently used drug for induction of general anesthesia. It

is safe, reliable, and relatively inexpensive. There are, however, a few absolute contraindications for its use (eg, barbiturate sensitivity and hereditary hepatic porphyrias.[6]) Diazepam has been used as an alternate to thiopental in these cases. Diazepam, unlike RO 21-3981, is not water soluble. The organic solvents used to make diazepam soluble cause pain on injection and subsequent thrombophlebitis.[7] RO 21-3981 was developed as a water soluble benzodiazepine with no organic solvents necessary. RO 21-3981 is thus thought to be a possibly superior alternative to diazepam for induction of anesthesia.

RO 21-3981, when used for induction of general anesthesia, was effective and safe in the 24 study patients. Patients went to sleep smoothly following loss of lid reflex, and the mask was placed on the patient's face without response. If tracheal intubation was planned, loss of lid reflex was, however, a poor sign of adequate dosage. Although none of the patients recalled intubation, a number of patients, all of whom received an induction dose of 7.5 to 15 mg of RO 21-3981, made seemingly purposeful clutching or grabbing movements with their hands at the onset of muscle fasciculation from succinylcholine. One patient who had d-tubocurarine 3 mg 3 minutes before succinylcholine to prevent fasciculation made similar hand movements but did not have gross fasciculations, giving credence to the thought that we were seeing purposeful movements and not early fasciculations. These movements did not occur in 2 subsequent patients who received larger doses (15 to 25 mg) of RO 21-3981 in 1 injection, suggesting that the purposeful movements may have been the result of inadequate induction dose. Maintenance of anesthesia and recovery were uneventful. Vital signs remained stable throughout the operation and most patients were awake on arrival in the recovery room or shortly thereafter.

RO 21-3981 has many possible uses in anesthesia. As a premedicant, its amnesic, sedative, and anxiolytic properties are profound. For induction of anesthesia, RO 21-3981 may be more advantageous than thiopental in terms of smoothness of induction in cases in which a face mask will be used. In patients in whom intubation is planned, RO 21-3981 does not offer an obvious advantage over thiopental but may well be an effective alternative. The lack of pain on injection and absence of thrombophlebitis may be valuable properties when compared with diazepam. Further clinical investigation as well as controlled studies of the cardiovascular and respiratory effects of this drug are indicated to delineate more clearly its future role in clinical anesthesia.

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Pharmacology, Pressures and People

Twelfth Annual Becton, Dickinson and Company
Oscar Schwidetzky Memorial Lecture

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At a faculty meeting recently a colleague expressed to me the simplicity of my job as chairman of the Department of Anesthesia. In what I hope was a joking manner, he said, "You need only know a bit of pharmacology, how to measure blood pressure, and then find enough people to run your operating rooms." After commenting about his lack of insight, I dismissed his remarks. Subsequently, I rethought them and realized that in the broadest sense he was absolutely correct. Generously interpreted, his remarks cover an extremely broad area. Certainly we are deeply involved in pharmacology, and we are constantly committed to the measurement and evaluation of blood pressure and its components. Our consuming interest in manpower today says much as to the most important of these 3—the personnel to carry out the tasks we have. These 3 problems are sufficiently complex to challenge the best of us. At least my colleague's remarks provide me with infinite leeway when pressed to select a title for a presentation such as this.

Age allows one to view the past from a broad point of view and provides an opportunity to relate the past to the present and to the future. Perhaps more important, it allows one to relate his honest feelings with less threat of loss of livelihood or social status. This I hope to do in a constructive way. It is my intent to be somewhat critical because little good will come from self-praise. It is actually my intent to be supercritical of some of the unsatisfactory fringe of our specialty. Being critical of our unsatisfactory fringe is obligatory for the best professional activity. The difference between a champion and a 2nd-place finisher in a race is often less than one-tenth of a second. One stroke's difference in a golf tournament is the difference between fame and anonymity. The successful are not satisfied with 95 percent good results. We are now mature enough to work for a higher degree of perfection. We must face the fact that there are still problems with our pharmacological perception and with our management of many pressures and the practice patterns of our people. Perhaps most importantly, there are problems with the interaction of the 3, for this interaction is what constitutes the practice of anesthesiology. Let's consider what we've done—where we are—and what we might do.

Development in pharmacology is, of course, basic to our specialty. The parade of individual drugs which have been observed during my professional career is too large to list, but it is possible to consider some of the general changes that have developed. The change from the relatively simple ether anesthesia to the currently available variety of drugs represents a steady and unrelenting change which probably falls in the category of progress. While one can list many specific advantages claimed by newer and current drugs, I believe there are 3 aspects which are undeniable and perhaps

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represent the only certain advances the new drugs offer when compared to our previous armamentarium. These are patient comfort, ease of administration, and the nonexplosive nature of compounds used today.

Stating these 3 as the only proven and certain advances is not to minimize the advances. These are of great importance. Certainly patient comfort is important; that is why we are here. We now have a generation or more of citizens who have experienced anesthesia as not being unpleasant. Society no longer has the "choking and smothering" concept of anesthesia that was dreaded a quarter of a century ago. Today nausea after anesthesia is almost uncommon. That is real progress. Ease of administration is certainly an allowable advantage to the anesthesiologist. In addition to making life more pleasant, this enables us to devote attention to problems of more complex natures. The nonexplosive aspect of anesthetic agents has aided important new surgical and monitoring technics, and has removed at least 1 hazard from the operating room.

It was once common to emphasize characteristics of the desired ideal anesthetic agent. Although we have not completely achieved that ideal to date, we can now anesthetize ill premature infants for the most serious and life-threatening congenital anomalies. We can anesthetize the severely traumatized and the moribund patient. We can anesthetize the most frail and disordered of our senior citizens for prolonged and major surgery. In all of these categories, excellent recovery is not only possible but expected. Today's pharmacological agents, then, must be wonderful tools. As a matter of fact, they are so good that improvement in their overall goodness is predictably very limited for the future. Progress to today's state has been steady and rapid in reducing side effects and untoward reactions of drugs. Agents are increasingly predictable in their effect and control. The chemist and pharmacologist have provided us with antagonists to drug action which now allow us specific and powerful reversal of much of the badness that we have produced. This is almost too good to be true.

Perhaps of more interest are changes in pharmacologic concepts. The idea was once widely accepted that anesthetic agents were inhaled and underwent some mysterious mechanical marriage within the central nervous system and then were divorced and exhaled unchanged. We have now learned that biodegradation occurs to a surprising degree and this biodegradation is not a meaningless happening. We now identify specific effects, sometimes undesirable, which are rather closely related to anesthetic metabolism and metabolites.

We have developed our own basis for potency to place the study of comparative pharmacology on a more rational basis. The MAC concept has made foolish some of the statements we learned a quarter of a century ago concerning the relative pharmacological differences of agents in use.

The entire study of pharmacokinetics, which is a somewhat sophisticated name for uptake, distribution, and elimination, has expanded greatly. This provides a much greater basis for understanding drug action, for managing drug administration, and certainly for development of new drugs.

The maturation of research deserves special emphasis. Research in pharmacology of anesthesia has been advanced by developments in technology, in sensing elements, and in statistical methods and data handling beyond our wildest hopes a few years ago. This pharmacologic research has developed with an increased regard for human subjects. Our research is progressing to the molecular and subcellular level to the extent that there are those among our leaders who state that the only good and basic research is at this latter level.

Research has many spinoffs, and an academic department without research or a scientific society which does not recognize research will live—if at all—in an unhealthy and undesirable intellectual environment. A good teacher who doesn't appreciate research probably does not exist. To be able to really teach, one must recognize what is known, realize what is not known, and properly identify each to his students. He should be able to devise questions the answers to which are obtainable. This mental attitude is, in fact, the essence of research.

While research has obviously lead to and developed the previous advances, it has had other important but less direct contributions to our specialty. Research has attracted many fine minds to this specialty and retained these fine minds in productive careers. Research has given prestige to our societies and to our journals. Research has improved our status in the medical communities in which we live. It has improved

and increased our range of activities and capabilities in the operating room, in the intensive care unit, and in the classroom. These changes mark the normal progress of a specialty. We have done well and we should indeed be proud.

To look at the 2nd element of my title, we have also progressed far beyond the early concepts of blood pressure measurement and monitoring. We have expanded pressure measuring to include airway pressures and the partial pressures of respiratory gases within the bloodstream and tissues. Increasingly, we are pointing our pressure sensors at the central nervous system. Developments in and from this widespread pressure monitoring have been rapid and provide us with much about which we can project and pontificate. We have been leaders in development of many physiologic concepts of relationships between pressure and perfusion. We really started the refinements and sophistication of pulmonary ventilation under adverse circumstances. We have contributed greatly to development of respiratory and circulatory equipment. The clinical results of these have been extremely rewarding. Intensive care units and recovery rooms often provide exhibits of circulatory and respiratory physiology which could only be displayed in relatively advanced laboratories a few short years ago. The application of continuous positive airway pressure, which originated in a department of anesthesia, provided the major breakthrough in the treatment of respiratory distress syndrome of infancy. The expansion of blood pressure monitoring to include right-sided circulatory pressure monitoring now allows us to take a more sophisticated look at perfusion rather than at pressure alone. These developments have facilitated advancement and successful expansion into surgical activities which were almost science fiction 20 years ago. All problems are not solved, but progress has been remarkable, interesting, and rewarding.

Accompanying our new concepts and practices has been development in equipment for both generation and measurement of pressures. Crude, cumbersome, and unstable equipment has been replaced with shiny, sophisticated, reliable, and expensive respirators, monitors, and analyzers.

As one turns to people, the same change in model has not been noted. The person administering anesthesia looks the same. True, the hair or the skirt may be longer or shorter and there is often an increased amount of gray in the hair which protrudes beyond the confines of the scrub cap. Affluence has perhaps changed some external dimensions and profiles of the administrators but there have been no basic model revisions.

However, within the old chassis there are definite changes. The mind is better trained. Residency programs have improved from a time when a faculty of more than 2 was an oddity. Large faculties and extensive curricula are common. The background of information has "exploded." We are interviewing an ever increasing quality of resident applicants and we can expect this to continue in the coming years. We are more involved with continuing education; we are conscious of the need to learn, to develop, and to keep up with developments in related fields. The unchanged external model has effectively adapted its internal workings to the progress in drugs, in physiologic concept, and in equipment design.

What then is the problem and where is need for the promised criticism? Can this pleasant parade of progressive improvement be the basis for criticism? Can so much goodness actually be a cause for problems? With the fine agents we now have, with the ability to obtain information from and about patients and with the educational training system we now have, anesthesia should be nearly free of catastrophic and disastrous complications except in the extremely high risk and unusual situation. Our more sophisticated research should produce means of greatly improving patient care. The combination of all these developments should result in more efficient, less expensive delivery of anesthesia with nearly a flawless safety record. However, there is much evidence in plain view to the contrary.

We face a very challenging situation. Having done all this good, we turn to receive the applause of society—but the response is not entirely laudatory. Mingled with the applause, we receive extremely careful scrutiny and no small amount of attack. Our government attacks us in the sensitive area of 3rd-party payment. We are attacked by others who say we and technicians are inseparable in terms of tasks done. The government agencies concerned with accreditation provide a classic catch-22 by insisting on firm quality control and then accusing us of restraint of trade because of our restrictions. Our research dollars are increas-

ingly hard to obtain, partially because of a charge of failure to produce. Society attacks our image on television and from the printed page. They rightfully object to increased and increasing costs. They demand increased information and safety. The malpractice crisis reflects much of this critical posture.

We have the ability and information to face this scrutiny and answer the challenges if we do the best we can. However, we face the distinct possibility of failure if we ignore the problems and disregard the legitimate questions which are raised. We must admit the existence of problems and imperfections.

I would like to now discuss some of my thoughts—why I think the fringe of imperfection continues to exist. This obviously is done with a certain trepidation. It is against my basic upbringing to speak critically to my hosts. However, there is good reason to be honest. I know these ideas are shared by many of our leaders; and I respectfully submit them for careful consideration.

There are problems in our pharmacologic perception. There are misapplications from our pressure probing. There are misadventures in our practice patterns.

It is at first surprising to find that the pharmacologic developments of which we are so proud and from which we benefit so greatly have themselves done something to the practice of anesthesiology which results in complications. As a specific example, antagonists may be considered. The mere presence and availability of an antagonist reduces the scrutiny and care necessary for administration and control of the agonist. I hear as a common statement in practicing circles that another dose of narcotic is chosen or that larger doses of relaxants can be given because "we can always reverse it at the end." It is therefore not unexpected or surprising to find a mismatch of agonist and antagonist in the recovery room or intensive care unit. The complications resulting from this mismatch are too obvious to need a description to this group. Despite claims to the contrary, the partially paralyzed patient requiring prolonged mechanical ventilation in the recovery room following large doses of relaxants is not a rarity. The differences in time constants of narcotic and narcotic antagonist have produced many hypoventilated postoperative patients. All too often this means an increasing reliance upon respirators and indwelling endotracheal tubes. All of these may extract a price that will occasionally be high.

The substitution of diethyl ether by drugs such as succinylcholine, methoxyflurane, and halothane has lead to specific toxic problems which are so insidious in their onset that the avoidance of complications is difficult. In succinylcholine, we may have produced our most dangerous drug because of its peculiar ability to produce serious and life-threatening complications even when given in *proper therapeutic amounts.* Errors of metabolism make such events as hepatic and renal toxicity or prolonged effect of drugs difficult to predict. Such untoward reactions were not part of the limited armamentarium of N_2O and ether.

In spite of these shortcomings, it is quite wrong to consider that most complications are to be blamed on the drugs themselves. Anesthetic drugs do not appear to be highly lethal. On the contrary, their performance testifies to great safety and indeed forces us to look for other causes of catastrophe.

As sacrilegious as it sounds, there may be some undesirable aspects concerning our pharmacologic research. Some of us are guilty of research for the sake of research. We find an idea which is attractive to a funding source, and this becomes an excuse for its performance. We develop a model and study an endless number of minor variables. We have explored at considerable expense to society some pharmacologic aspects of anesthesia beyond reasonable clinical reward. This may be honorable and promotable academic and intellectual activity and be quite acceptable in a society with an infinite supply of dollars. This we do not have at the present time. There is a compelling need to establish priorities and conduct our investigations accordingly, especially when investigations are performed at society's expense.

Of particular concern is a tendency for pharmacologic research to reveal an isolated function of a drug and to then prescribe a place for this finding in our care of patients in the future. Such prescription is often done without comparing the suggested new practice with the existing alternatives. Let me cite an example. It was perhaps reasonable in an earlier day to teach that ether was contraindicated for diabetics simply because the blood sugar was elevated. It was also acceptable to teach that ether was strongly indicated as anesthesia for

asthmatics simply because it produced bronchodilation. We could accept the simple and unproven implications of these isolated facts in the immature days of our specialty. We now demand a more sophisticated specialty to handle the dilemma of anesthesia for the asthmatic diabetic. It is disappointing that the former practice continues, however. Recently, the fact that halothane anesthesia results in an increased cerebrospinal fluid pressure has been loudly touted as a reason to avoid this agent for craniotomies. This recommendation appears to be based on the finding that cerebrospinal fluid pressure rises temporarily with induction of halothane anesthesia. It is not at all founded on evidence that patients have suffered or that complications have arisen as a result of this phenomenon. The recommendation to avoid halothane is made in spite of tens, perhaps hundreds, of thousands of remarkably successful craniotomies done during halothane anesthesia. In fact, a period of rapid advancement in neurosurgery coincided with the era of halothane. I find this reasoning unacceptable, especially when one considers that alternatives suggested have within them hazards of their own.

At great expense to society, myocardial depression by anesthetic agents has been measured and remeasured by many means. Until recently little or no research has gone into the determination of whether controlled myocardial depression is harmful, or might, in fact, be beneficial. Yet recommendations to avoid myocardial depressants persist in the face of tremendous clinical success using the most potent of myocardial depressants on patients with severe heart disease.

William Harvey, in his 17th-century book describing circulation, states: "Careful observation is needed in every discipline and sensation itself is often to be consulted. One's own experience is to be relied upon, not that of someone else." In another age, the same idea was expressed: "The research method in use today is quite unsuited and misleading since many inquiries are not what things are but what is said about them by others. I therefore whisper in your ear dear readers, that you weigh in exact balance of experience whatever I treat of in these essays. That indeed you use these only insofar as you find them most firmly corroborated by direct evidence of your own sense." This was written by Aristotle. We will do well to temper the results of today's investigators with this advice from the past.

Expansion and progress in the area of pressure and its evaluation perhaps provide less area for criticism, but it is not entirely guiltless. We must at least ask the questions: Have we overcomplicated our procedures in the operating room? Does this overcomplication dilute our attention to more basic details? Do we create a false sense of security by having super-monitoring? We do know that these tendencies are tremendously expensive and have done a great deal to increase the cost of health care delivery. We further know that these are at least a part of the basis for the increasing tyranny of standards with which we are faced.

A critical look at our activities in pressures necessitates a re-evaluation of uses of IPPB. We are among the most active perpetrators and purveyors of the prophylactic and semiroutine use of this practice for many types of surgical patients. Almost all inquiries into usefulness of this practice have indicated no benefit. Yet it continues with little challenge in most hospitals at tremendous cost in dollars and space.

To me the matter of most concern in this critical look at the trilogy of pharmacology, pressure, and people is that of the practice patterns of those of us practicing anesthesia. On one hand, we can see extremely good results from the practice of anesthesia. A community hospital, with careful and competent anesthesia personnel, performs hazardous surgical procedures on very ill patients and experiences remarkably good results. This proves it can be done. On the other hand, in some quarters there is a persistence of alarmingly bad results.

My observations lead me to a most serious charge to the specialty. I find strongly suggestive evidence that some practitioners of anesthesia are not sufficiently challenged by their tasks to maintain a satisfactory degree of vigilance. Perhaps this is our greatest problem.

The evidence is found in at least 3 recently published reports concerning cardiac arrests and deaths related to anesthesia. The evidence is found in the malpractice crisis, part of which is probably due to actual malpractice. The evidence is found in reviewing complications at staff conferences of many hospitals.

Review of the reports by Dr. Derek Wylie of St. Thomas Hospital in London,[1] by Dr.

Gordon Taylor of Stanford University,[2] and by the Australian Special Committee Investigating Deaths Under Anesthesia[3] reveals a surprising and common finding. There is a disturbing incidence of catastrophic complication occurring in fit patients anesthetized by trained anesthesia personnel for less than complex surgical procedures. In one report[2] the results of resuscitation efforts are appalling—again supporting the possibility that lack of attention and resulting early diagnosis are part of the basis for this grim finding. In these circumstances we are hard pressed to blame the disease, and all of us would deny incompetence. I do not say all or any are malpractice. There are unusual electrolyte abnormalities and abnormal responses to drugs, but probability says the latter are indeed rare.

I am asked to review many malpractice cases and during the past 3 years have reviewed cardiac arrests associated with anesthetists leaving the operating room, more than 1 arrest because of prolonged disconnection of a ventilator, or aspiration of gastric contents during induction of emergency anesthesia when none of the accepted preventive measures were employed, and at least 2 arrests in which the surgeon had to diagnose the arrest. These are anecdotal but are representative examples of a sizable group. Certainly we cannot blame the drugs or the equipment for these events. Is it not possible that the ease of administration combined with the vastly improved training result in a situation in which anesthesia for "regular surgery"—for fit patients—can be dangerously boring? We need not be afraid to admit this unless we ignore the answers. Boredom is not limited to anesthesiologists. The effects are often more striking, however. If a bored and tired surgeon fails to perform a rectal examination, his patient's death from carcinoma of the rectum is remote in time and not readily traceable to the failure to act. Not so for the physician who fails to check a flowmeter or a ventilator connection. So far, improved monitoring has not avoided the problem. Perhaps it adds to the ease of administration and actually contributes to the problem. I am told that industry has found people overtrained for their tasks are accident prone and poor performers. Does this suggest a necessary change in our practice patterns? It would be very difficult to conceive of purposely degrading our residency programs. Must we therefore reassess use of non-physician personnel? This might involve some gross restructuring. It is most important that we do it, not have it done to us.

There are other observations which do not shed glory. In some areas of the country there is a high incidence of free-lance practice where anesthesiologists work for varying periods of time in a large number of hospitals. They assume no—or at least a minimal—role in their medical community and thus contribute little of what anesthesia has to offer in improvement of hospital practices. There are hospitals where obstetrical anesthesia is hardly available but standby coverage, during daylight hours, is readily provided for local anesthesia.

Many of my colleagues who are professors have essentially abandoned the practice of anesthesia. In one school I am told a reward is offered if the professor is actually found in the operating room. Such professors must be unduly removed from the problems they were selected to prevent or solve. These observations will not do us a favor as they are scrutinized by others.

Having listed and discussed my prejudices as to some of our most pressing deficiencies, I have an obligation to suggest remedial action. This is not easy. There is no magic solution. I have the following general plan.

1. We must determine realistically what the situation is. A search for the real complications related to anesthesia needs to be made, regardless of its difficulty.

2. We must direct our researches—pharmacologic and social—at the offending items.

3. We must conduct our practices with cost to society in mind. The government must cooperate and be informed with real cost-benefit data.

4. We must assess our functions realistically. We must be ready to change our habits and involvement to guard against boredom from lack of challenge, from disaster due to lack of vigilance.

These are not comforting thoughts, especially when answers are not readily accomplished. There is some comfort to be gained by realizing how far we have come and how very well we actually do. I have no doubt that the incidence of catastrophe has been reduced and that anesthesia as a major cause of surgical mortality has been eliminated. Conditions once absolute contraindications to surgery are now indications for the most major of surgical interventions.

The previously outlined progress came be-

cause our predecessors faced different but equal problems honestly and with continuing effort. There remains the necessity to face the situation as it exists, not as we wish it to exist. If we persist in the patterns which create this undesirable fringe, the fringe will persist or perhaps grow.

I should perhaps apologize for making unpleasant sounds, but I really believe they must be made again and again. Goethe, the German writer and thinker, has said, "That which we won't admit—that which we hate to hear—is precisely what must be said again and again."

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Hemodynamic and respiratory effects of spontaneous ventilation with continuous positive airway pressure (CPAP) and mechanical ventilation with positive end-expiratory pressure (PEEP) were compared in 9 patients who had adult respiratory distress syndrome. The patients were capable of maintaining spontaneous ventilation (tidal volume > 300 ml and $Paco_2 < 45$ torr). Arterial and mixed venous blood gases, cardiac output, O_2 delivery and consumption, pulmonary artery pressure, and pulmonary wedge pressure were measured in 11 instances with each patient on 5 or 10 cm H_2O CPAP or PEEP, and in 9 instances with each patient on the ventilator but without PEEP. During CPAP, when compared to PEEP at the same level of end-expiratory pressure, mean Pao_2 increased significantly ($p < 0.05$) and mean physiological shunt decreased ($p < 0.05$). In 9 of 11 instances, cardiac output was higher on CPAP than on a corresponding level of PEEP. Thus CPAP was more effective than the same amount of PEEP in improving arterial oxygenation without adversely affecting cardiac output. *(Shah DM, Newell JC, Dutton RE, et al: Continuous positive airway pressure versus positive end-expiratory pressure in respiratory distress syndrome. J Thorac Cardiovasc Surg 74:557-562, 1977)*

A New Nerve Stimulator for Monitoring Neuromuscular Blockade and Performing Nerve Blocks

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A new stimulator is described with characteristics designed to take advantage of recent knowledge of the pharmacology of neuromuscular relaxants and events involved in normal neuromuscular transmission. The stimulator has proven as useful in performance of peripheral nerve blocks as in monitoring neuromuscular blockade.

Key Words—EQUIPMENT, nerve stimulator. NEUROMUSCULAR RELAXANTS, measurement of response. MONITORING, nerve stimulator.

In 1965, Katz[1] described a peripheral nerve stimulator designed specifically for clinical use in evaluating the status of neuromuscular blockade. In that article Churchill-Davidson was quoted as stating, "The only satisfactory method of determining the degree of neuromuscular block is to stimulate a motor nerve with an electrical current and observe the contraction of the muscles innervated by that nerve."[2] Since that time, the use of neuromuscular blocking drugs has increased and numerous studies have been performed to improve the understanding of these blocks and to develop better clinical tools for monitoring blocks and evaluating their reversal. Nerve stimulators have been increasingly used for this purpose. Further, nerve stimulators have also been gaining popularity as a means of locating nerves in performing peripheral nerve blocks. Prior to beginning this project, we reviewed the nerve stimulators available. Existing nerve stimulators, while useful for the functions described, did not really have characteristics that took advantage of more recent knowledge and its applications. Therefore, new criteria were established, and a new stimulator has been designed and is now in clinical use (see figure and table 1 for output characteristics). The stimulator is powered by a 9-volt transistor battery. The following sections will describe its characteristics and use for both monitoring neuromuscular blockade and performing peripheral nerve blocks. (It should be noted that

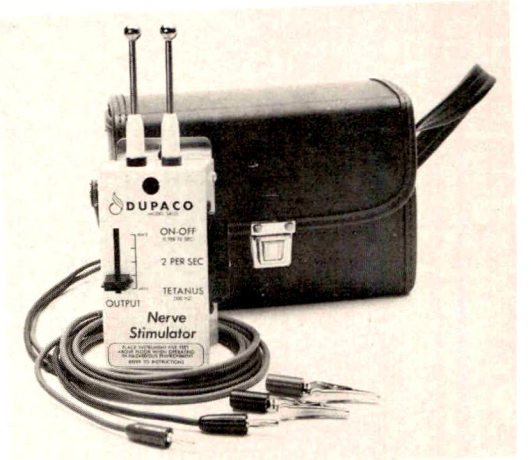


FIGURE. Nerve stimulator described in text (photo courtesy of Dupaco Co., San Marcos, California)

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TABLE 1
Output Waveform Characteristics and Output Peak Voltage for Various Loading Resistances

Output waveform characteristics

1. 220: open-circuit voltage
2. Rise time: 0.05 msec
3. Pulse width: 0.6 msec
4. Decay time: 0.1 msec

Output peak voltage for various loading resistances

Output load, ohms	Output peak voltage, volts
100	2.5
470	11
1,000	24
3,300	60
5,600	82
10,000	120
30,000	170
50,000	180
100,000	200

other nerve stimulators have recently appeared on the market which possess some, but not all, of the characteristics of the unit described herein. A detailed critique and comparison of these are beyond the scope of this paper.)

MONITORING OF NEUROMUSCULAR BLOCKADE

In a recent review of antagonism of neuromuscular blockade, Miller indicated, "Since the last review of the pharmacology and clinical use of muscle relaxants in 1959, almost half of the case reports in anesthesiology involving muscle relaxants have been concerned with antagonism of neuromuscular blockade."[3] Ensuring adequate return from or reversal of such blockade is obviously of great importance. Technics developed for this purpose include various modes of nerve stimulation with observation of muscle response; ventilatory function; and direct evaluation tests, such as head lift and grip strength.

It is important to note that a large percentage of neuromuscular receptors must be blocked before transmission fails. Paton and Waud[4] showed that only 20 to 25 percent of the receptor pool is necessary for transmission to all of the fibers in a muscle. Further, Waud and Waud showed that "For recovery of the diaphragm, roughly 5 percent of the receptors must be free in the dog and 15 percent in the cat. For recovery in the tibialis, the values are 10 percent and 25 percent respectively. Thus, the diaphragm needs only about half as many receptors as the tibialis anterior for a normal twitch response."[5]

Since nerve stimulation, head lift, and hand grip all test peripheral function, one would expect these tests to be conservative concerning diaphragm function. On the other hand, direct tests of diaphragm function such as tidal volume, expiratory flow rate, vital capacity, and inspiratory force may be normal under normal neurostimulation with a low percentage of free receptors; however, with the same percentage of free receptors, if the neuromuscular system is stressed, ie, by partial obstruction, excitement, and tachypnea, then transmission and hence ventilation may fail. Failure could also occur with changes in temperature or electrolytes, or drop in transmitter output.[6]

While head lift and hand grip may be adequate tests of return of neuromuscular function, they require patient cooperation. In many situations, it is desirable to ensure return of normal neuromuscular function before the patient is fully awake and cooperative; hence, nerve stimulation in the still depressed patient appears to be the technic of choice. The following discussion will be directed at use of nerve stimulation to monitor nondepolarizing neuromuscular blockade; depolarizing blockade will be commented on later.

Three modes of nerve stimulation have been used: single twitch, tetanic rates of 30 to 100 Hz, and train-of-four. Using receptor occlusion technics in animals, Waud and Waud[6,7] have shown that the 3 modes of stimulation indicate "normal" function at quite different levels of free receptors, as shown in table 2. The data shown represent the approximate percentage of neuromuscular junction receptors which can be blocked so that a supramaximal electrical stimulus of the various types shown will still produce a normal muscle response (as recorded with a force transducer). Single twitch and sustained tetany at 30 Hz are seen to be equally sensitive in detecting the degree of block reversal. Train-of-four (2 Hz for 2 seconds) with no detectable fade is slightly better. In all of these cases the margin of safety in terms of the studies cited

TABLE 2
Maximum Percentage of Neuromuscular Junction Receptors Blocked When Supramaximal Electrical Stimuli of Nerve Produces Normal Muscle Response[6,7]

Stimulus	Receptors blocked, %
Twitch	75-80
Tetany— 30 Hz	75-80
100 Hz	50
200 Hz	33
Train-of-four	70-75

would be small for the peripheral muscles tested, although presumably larger for the diaphragm. Normal response without fade to tetanic stimulation at 100 Hz and 200 Hz clearly provides a much greater margin of safety.

The train-of-four technic as developed by Ali and coworkers,[8-11] while apparently not much more sensitive than the single twitch, has a marked advantage in that no preblock control is needed; the ratio of the 4th to the 1st twitch quantifies the block. The train-of-four technic also has an advantage over tetany in that it is not nearly as painful if applied to an awake patient.

More recently, Lee[12] has developed a more easily used train-of-four technic which does not require force or motion transducers or recording equipment. He compared the point at which each twitch in the train-of-four was no longer visible with the percentage of neuromuscular block as defined by the ratio of the magnitude of the first twitch in the train to the magnitude of a preblock control twitch. He found that the visual disappearance of the 4th, 3rd, 2nd, and 1st twitches corresponded with approximately 75, 80, 90, and 100 percent block. Lee encouraged use of this technic as a means of attaining a controlled level of block, ensuring an adequate block, yet at a reversible level; he points out that "Clinically profound abdominal relaxation can be achieved with 80 to 90 percent block in most cases,"[13,14] and "Satisfactory reversibility is possible with 5 percent recovery (ie, 95 percent block) and greatly facilitated if spontaneous recovery has attained 25 percent of control."[15,16] His technic is designed to maintain the neuromuscular block within this range.

In light of the preceding discussion and previously established criteria,[1] the following characteristics were incorporated into the nerve stimulator described herein:

Tetanic Stimulation at 100 Hz—As determined by Gissen and Katz,[17] Waud and Waud,[6] and acknowledged by Miller,[3] sustained tetany at this frequency provides a reliable index of recovery from competitive neuromuscular blockade, with a significantly greater margin of safety than that obtainable with 30-Hz stimulation.

Twitch Stimulation at 2 Hz—This makes possible the use of the train-of-four technic, particularly as described by Lee,[12] for controlling neuromuscular block at adequate yet reversible levels. While the margin of safety for determining adequacy of subsequent reversal is not great with this technic, tetany at 100 Hz as described above can be used for this purpose.

Continuous Standby Mode with Stimulation at 0.1 Hz (1 Stimulus Every 10 Seconds)—Katz[1] advised continuous monitoring for minute-to-minute control of muscle relaxation. The standby mode helps ensure continuous awareness, indicating "deepening" or "lightening" of the block. (See, eg, Miller[3] for intraoperative factors which may alter neuromuscular block.) The standby rate of 0.1 Hz was chosen both because Lee[12] states that restoration of steady state requires at least 10 seconds of rest prior to the train-of-four, and to minimize possible alteration of conditions at the neuromuscular junction over long periods of use.

While this discussion has been directed at the use of the nerve stimulator in intraoperative nondepolarizing neuromuscular blockade, it is also useful, as pointed out by Katz,[1] in (1) assessing the nature of a block, ie, Phase 1 depolarizing or Phase 2 nondepolarizing;[11,18] (2) determining the role of muscle relaxants in causing postoperative hypoventilation or apnea;[11] and, of course, (3) monitoring depolarizing blocks.

Lee[18] has studied the development of dual neuromuscular block with the depolarizing relaxant suxamethonium (succinylcholine), and has found train-of-four stimulation useful in distinguishing between Phase 1 and Phase 2 block. In a study of 7 individuals he found transition from Phase 1 to Phase 2 to occur after 2 to 4 mg/kg of suxamethonium, and that a Phase 2 block was established after 3 to 5 mg/kg. He found the transitional zone to be surprisingly narrow

but easily detectable by monitoring the response to train-of-four nerve stimulation.

PERFORMING PERIPHERAL NERVE BLOCKS

Nerve stimulators have found increasing application as a means of locating nerves in the performance of peripheral nerve blocks. Traditionally, such blocks have depended upon patient cooperation in reporting paresthesias elicited by the physician. Koons[19] points out that such blocks have often been neglected "because of: (1) lack of consistent success; (2) time needed to perform this type of anesthesia; (3) discomfort experienced by the patient and; (4) limited duration of the block." In recent years many workers have made use of electrical stimulation through the injecting needle to more simply and accurately locate nerve trunks for both single bolus[20-25] and continuous[19] technics. Montgomery, Raj, Nettles, et al[24] demonstrated that with proper technic virtually any hollow metal nerve may be used and that sheathing all but the tip with insulation is unnecessary. The technic described by Raj and coworkers[24,25] has been used with good success at this institution; one recent example was the use of a nerve stimulator to perform a femoral-sciatic block for open-reduction internal fixation of a compound fracture in a trauma patient who was responsive only to painful stimuli. The block was accomplished without difficulty and without interfering with observation of the patient's mental status or requiring general anesthesia in a patient with possible cervical spine damage and a full stomach.

The technic used at this institution, essentially that of Raj et al, is summarized as follows.[24,25] The ground electrode* of the nerve stimulator is attached to the skin at a site remote from the block site, using either a subcutaneous needle electrode or an adhesive (eg, ECG) electrode. After skin preparation, a wheal is raised with local anesthetic above the block site. An unsheathed needle (eg, 1-inch, 25-gauge for axillary block; 3½-inch, 22-gauge spinal needle for infraclavicular brachial plexus block) is introduced through the skin wheal and appropriately directed but only slightly advanced. Intravenous extension tubing attached to a syringe containing the desired anesthetic is attached to the needle. As Raj described his technic, the nerve stimulator is set to deliver 6 to 8 volts (consult technical data accompanying nerve stimulator); the stimulating electrode is then attached to the needle. With continuous stimulation at 2 Hz, the needle is advanced until movement of the muscles supplied by the sought-after nerve is observed. It should be noted that muscle groups adjacent to the stimulation electrode may be directly stimulated, and this movement must be differentiated from that of the desired muscles. Maximal stimulation is not yet sought.

The voltage is reduced to 2 to 4 volts and the needle advanced until maximal muscle movement at minimal voltage is attained. This may require withdrawal and readvancement at different angles. In our experience, there is little if any discomfort to the patient at this level of stimulation, but excessive needle manipulation should be avoided. One does not actually need to know the precise values of the stimulator output. Our own clinical technic has been to start with the output set just below the level at which tetanic stimulation can be felt with the electrodes held between the fingers of one of our own hands. Higher levels of stimulation can be quite uncomfortable to the patient. We emphasize again that there should be little if any discomfort to the patient with appropriate technic. Motor response can be elicited at stimulation levels which do not sufficiently affect sensory response to cause the sensation of pain.

At the point of maximal response to stimulation, 2 cc of anesthetic solution is injected (it is important to hold the needle in position), and almost immediate loss of muscle response to twitch should be observed. If not, the needle should be repositioned to obtain maximal response and the test dose repeated. If the muscle response is blocked, the desired anesthetic dose is then injected.

Any nerve stimulator with variable voltage stimulation capability in the range of 1 to 2 Hz can be used to perform peripheral nerve blocks as described. However, most available units require continuous pressure on the twitch button. The nerve stimulator described herein incorporates a mechanical device which may be used to keep the twitch button depressed while a nerve block is being performed. A separate mechanical device rather than a continuous action switch was chosen to help avoid inadvertent long-term

*It should be noted that DC nerve stimulators exhibit polarity, and one electrode (the "stimulating" electrode) stimulates more readily than does the other (the "ground" electrode). For convenience, the stimulating electrode on the nerve stimulator described herein is color coded red.

continuous 2-Hz stimulation during neuromuscular block, which could alter neuromuscular junction conditions and also conceivably cause permanent nerve damage. (To the author's knowledge, however, this has not been demonstrated to occur.)

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A Compromise for Closed System Anesthesia

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Closed system anesthesia is economical, minimally, polluting, and conserves a patient's airway heat and moisture. Yet this method of anesthesia is not widely used because it is considered dangerous by many clinicians. We review the origins of that belief and then test the application of 2 schemes for administering potent agents in a closed system with CO_2 absorption.

We 1st employed Lowe's square-root-of-time uptake model in 30 patients, using halothane or enflurane. We found that the model provided a good starting point for learning to use the closed system. However, anesthetic concentrations were not accurately predicted.

Based on our experience with that model, we examined a simpler approach. We began each of 10 anesthetics using a semiclosed system, then closed the system. Only sufficient O_2 for metabolic demand and halothane were added to the closed system. The rate of halothane administration was the same for each patient. This approach proved clinically satisfactory, and the measured halothane concentration remained relatively constant during 45 minutes using the closed system.

Changing from a semiclosed to a closed system affords the advantages of the closed system 75 percent of the time, yet requires no extra tasks or equipment.

Key Words — ANESTHETIC TECHNICS, closed circle. EQUIPMENT, anesthetic circuits.

ANESTHESIOLOGISTS are increasingly concerned about the health hazards[1] and cost of anesthetics. Pollution of the operating room atmosphere and the cost of inhalation anesthetics could be reduced by using the smallest possible amount of anesthetic, that is, by employing closed system technics with CO_2 absorption.

HISTORY

Closed system anesthesia is not new; in fact, the technic is mentioned in the first volume of *Anesthesiology*.[2] Yet young anesthesiologists have had little experience with closed system technics, since their teachers often consider the closed system dangerous. Cullen recently pointed out that this position needs to be re-examined, since the closed system provides a good method of diminishing operating room pollution with anesthetic gases.[3] We will explore the origins of the belief that closed system anesthesia is inherently dangerous and evaluate 2 methods for administering volatile agents in a controlled manner with a closed system.

In 1958 the Copper Kettle® replaced less

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efficient vaporizers in anesthetic practice. Morris and Feldman discussed deaths which occurred when diethyl ether was delivered from the Copper Kettle and indicated that these deaths occurred because practitioners were not sufficiently aware of the high concentrations which these new vaporizers could produce.[4] Apparently many individuals delivered the metabolic O_2 requirement through the vaporizer for the entire course of anesthesia, thereby accumulating lethal concentrations of ether within the circle system. Feldman and Morris also examined the administration of halothane with the Copper Kettle and stated that delivery of accurate concentrations of this agent was possible. However, they warned that "caution is mandatory when adding potent vapors to a closed system since lethal concentrations . . . are provided by this type of vaporizer."[5]

At about that same time, several deaths resulted from use of halothane in a closed system. One of these was reported by Foster, who administered halothane from an in-circle vaporizer in unknown concentrations.[6] At one point during the anesthetic, at a setting of "6" on the vaporizer, the patient became hypotensive; when the vaporizer was returned to this setting later, cardiac arrest occurred and was followed by death.

Problems with halothane in a closed system resulted from knowing neither how much halothane was required nor how much was being given. When the inspired concentration was measured and maintained at a known value while delivering halothane from a Fluotec® vaporizer into a closed circle system, overdosing did not occur.[7] Unfortunately, no monitor existed at that time for measurement of inspired concentrations of anesthetic vapors under clinical conditions.

A series of articles in 1960 presented theoretical, laboratory, and clinical studies of closed system anesthesia with halothane. Since there was no adequate model for uptake and distribution of halothane, the studies did not yield clinically usable methods for administration of closed system anesthesia.[8-10] Hampton and Flickinger applied what was known about halothane uptake to administer the agent in a controlled manner with a closed system.[11] They thought that halothane uptake equaled 10 to 15 ml of vapor per minute over the course of several hours, and they reasoned that addition of 90 ml of vapor to a circle plus patient gas volume of about 6000 ml would provide a concentration of 1.5 vol %. Since they planned to add small increments of liquid halothane to a circuit, they arranged an injection port over a wire screen placed in the inspiratory limb of a circle system and injected liquid halothane onto the wire screen. They began with 0.4 ml liquid halothane (approximately 92 ml of halothane vapor) and then repeated injections of 0.2 ml liquid every 3 to 5 minutes as required by clinical signs. In this way they primed the system to obtain 1.5 percent and then delivered sufficient halothane to balance uptake. The inspired concentration remained between 0.8 and 2.0 vol %, and hypotension (to less than 80 torr systolic pressure) occurred in 27 of 300 patients. Because a patient might receive a relatively large dose of halothane with this system, the authors recommended that the system be flushed with O_2 at the end of the procedure to speed awakening.

The uptake model which Hampton and Flickinger used to derive their halothane dose was too simple. In 1962 Mapleson showed that at a constant inspired halothane tension, halothane uptake decreased markedly with time, especially during the 1st hour.[12] This was confirmed in the following year by Eger and Guadagni, who maintained alveolar rather than inspired concentration constant.[13]

In 1964 Eger and Epstein, in a discussion of hazards of anesthesia equipment, observed that, "used properly, semi-closed and closed absorption systems provide the advantages of economy, carbon dioxide removal, ease of observing and controlling ventilation, and minimal heat loss and drying. Rate of inflow gas into these systems is no longer crucial. Under certain conditions . . . they promote a stable anesthetic state."[14] To the above advantages we could add the approximate assessment of O_2 uptake, and the freedom from operating room pollution.

As better uptake and distribution models were developed, it became apparent that calculation of doses of anesthetics based on uptake would be difficult. Knowledge of such doses, however, is essential in closed systems where metabolic and anesthetic gases are supplied at rates which equal uptake by the patient, to maintain the system at constant volume and composition. The complex problems of uptake and distribution, in addition to reports of anesthetic deaths with halothane in the closed system

at a time when pollution by waste anesthetic gases was ignored, led to the demise of closed system technics. However, in a recent article, Barton and Nunn discussed the advantages of using closed system technic with N_2O, although they did not apply their method to the administration of more potent anesthetics.[15]

Lowe has stated that the complicated "true" uptake and distribution curve can be approximated by a much simpler one.[16] The rate of uptake of any agent approximately follows the inverse of the square root of time. This means that as time goes on, the amount of anesthetic taken up by the body decreases. The points in time between which equal amounts of anesthetics are taken up are squares of integers—0, 1, 4, 9, 16, 25, 36, 49, etc. Thus, the amount of anesthetic taken up during the 1st minute of anesthesia equals the quantity taken up during the next 3 minutes, which equals uptake for the next 5 minutes, etc. Lowe called the amount of anesthetic taken up during any one of these units of time the "unit dose."[17] An additional dose, called the "priming dose," is required to fill the 3 largest nontarget compartments—gas space of the anesthesia machine, gas space of the lung, and the blood compartment—in order to reach the target organ, the brain.

The following are Lowe's equations for obtaining the "priming" and "unit" doses:

Priming dose = $(Can) \cdot (Vc + FRC + \lambda \cdot V_B)$,

Where priming dose is expressed as ml vapor,

Can is the concentration of anesthetic in vol %,

Vc is the anesthesia circuit volume in dl,

FRC is the patient's functional residual capacity in dl,

λ is the blood-gas solubility coefficient of the anesthetic agent, and

V_B is the patient's blood volume in dl.

Unit dose = $2 \cdot (Can)\ (\lambda)\ (Q)$

Where unit dose is ml vapor,

Q is cardiac output in dl/min.

In our first group of patients we tested the accuracy and practicality of this model in the clinical setting. Based on that experience, we developed and tested a simpler approach—an intermittently closed system.

METHOD

Accuracy of the Model—Thirty men were included in the study, and endotracheal intubation and anesthesia with either halothane or enflurane was planned. Based on the clinical assessment of each patient, the desired exhaled anesthetic concentration was estimated and expressed as a MAC multiple. Typically 1.3 MAC, the ED_{95} for anesthetics,[18] was chosen and was approximated by administration of 65 percent N_2O (0.65 MAC) plus 0.65 MAC of halothane or enflurane. In some patients no N_2O was used. In applying Lowe's equations, we assumed that a 70-kg individual has a blood volume of 5.0 litres and a cardiac output of 5 L/min, and that function residual capacity (FRC) plus gas volume in the anesthesia circuit equal 6 L. For simplicity, the doses were assumed to be proportional to weight, so that doses for patients of other weights could be calculated by multiplying the 70-kg dose by $\left(\frac{\text{patient weight}}{70}\right)$. We allowed 9 minutes to attain the desired vapor concentration. Therefore, 1 priming dose and 3 unit doses (0-1 min plus 2-4 min plus 5-9 min) were administered during the first 9 minutes of anesthesia. This was accomplished by administering a constant flow of vapor equal to one-ninth of the sum of 1 priming dose plus 3 unit doses. Vapor flows after 9 minutes were calculated from the unit dose. The flow rates were recorded as a "program" for each anesthetic.

Our anesthesia machine had a Vernitrol® vaporizer and a Foregger Jumbo Circle® absorber containing soda lime, and had been checked for leaks and for the accuracy of its flowmeters. When N_2O was used, an O_2 analyzer (Harris-Lake) was placed in the exhalation limb of the breathing circuit, and the N_2O flow rate was adjusted in accordance with observed O_2 concentration.

Thiopental 3 mg/kg was used for induction of anesthesia, followed by succinylcholine 1 mg/kg to facilitate tracheal intubation. After intubation, a 16-gauge catheter was positioned in the endotracheal tube, its tip at the tip of the tube, for gas sampling, and the inhalation anesthetic was begun using the predetermined "program" for flow rates. As the anesthetic progressed, flow rates were adjusted in accordance with the program; and at 0, 1, 4, 9, 16, 25, 36, 49, and 64 minutes, samples of exhaled gas were drawn into glass syringes during the last half of an exhalation and analyzed for halothane

with a Beckman (Model #72-5) gas chromatograph. After 9 minutes flow rates were changed, as indicated by the program, immediately after samples were obtained.

Intermittent Closed System — Ten male patients were studied in whom anesthesia with N_2O, O_2, and halothane was to be employed. Anesthesia was induced with intravenous thiopental 3 mg/kg, and succinylcholine 1 mg/kg for tracheal intubation. A 16-gauge catheter was placed in the endotracheal tube for gas sampling and the inhalation anesthetic was begun, using a semiclosed system with a total flow of 5 L/min and 60 percent N_2O. A Harris-Lake O_2 analyzer was placed in the inspiration limb of the circle as a precaution during each anesthetic. The concentration of halothane delivered from the anesthesia machine was adjusted according to usual clinical criteria; ie, patient's response to stimulation, pattern of ventilation, blood pressure, and heart rate. Where appropriate, patients were paralyzed with d-tubocurarine and their lungs ventilated with an Air-Shields anesthesia ventilator. After 20 to 30 minutes, when vital signs and anesthetic state appeared stable, the system was closed. The N_2O was turned off, and the O_2 flow through the halothane vaporizer was decreased to 25 ml/min. The main O_2 flow was initially reduced to 300 ml/min and then adjusted as required to maintain constant system volume.

Samples of exhaled gas were obtained as described above just before the system was closed and then 5 and 10 minutes later, and every 10 minutes thereafter until the end of the anesthetic. Samples were analyzed for halothane with a Beckman gas chromatograph and for O_2 with a radiometer blood-gas analyzer.

RESULTS

Accuracy of the Model—Figure 1 is a plot of the mean and SD of observed exhaled anesthetic concentrations for all 30 cases, expressed as a percent of the "expected" concentration if the uptake model were accurate. In our 30 cases the concentration at 9 minutes was 148 ± 86 percent (mean ± SD) of that expected. The mean concentration remained essentially unchanged thereafter.

On 6 occasions departure from the calculated program was required because of arterial hypotension. In 3 of these the anesthetic concentration was at or below the calculated value at the time hypotension was noted. Modification of the program because of clinical problems was not required in any of the last 18 cases.

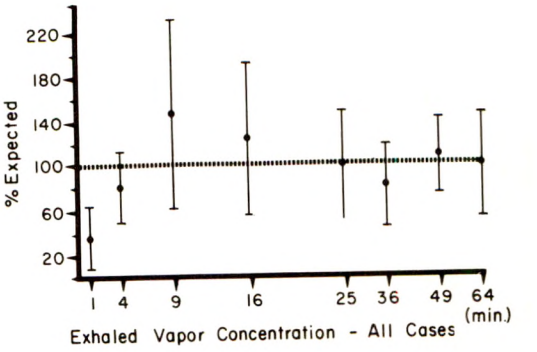


FIG 1. Square root of time technic. Exhaled anesthetic concentration, mean ± SD (percent of expected), as a function of time for 30 cases.

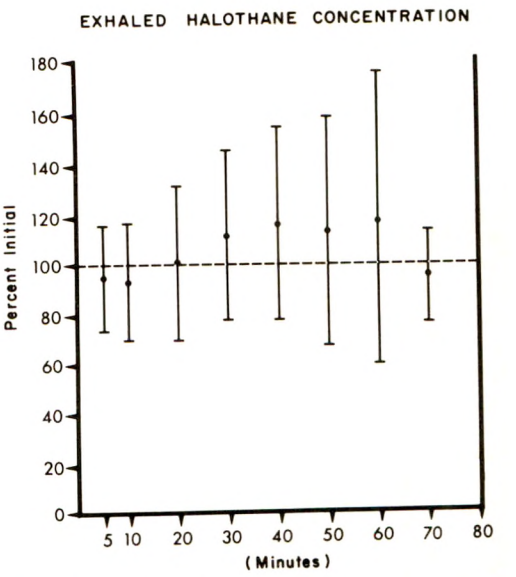


FIG 2. Semiclosed to closed technic. Exhaled halothane concentration, mean ± SD (percent of initial), as a function of time after closing the system.

Intermittent Closed System—Halothane concentrations were between 0.40 and 1.08 vol % when the system was closed. Figure 2 shows halothane concentrations, during the course of the closed system anesthetic, expressed as a percent of the concentration when the system was closed.

Oxygen concentration never decreased, but actually rose from 40 ± 2 vol % (mean ± SD) at the time the system was closed to 62 ± 3 vol % 30 minutes later and to 66 ± 4 vol % at 60 minutes.

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DISCUSSION

Our experience with the square root of time model revealed several problems. First, a physician must be familiar with the details of uptake and distribution as well as with the particular constructs of Lowe's model, namely the priming and unit doses. Those concepts and various assumptions are necessary to calculate doses which will be administered. While the calculation is not mathematically complex, it is time consuming even with an electronic calculator and requires additional preparation for the administration of each anesthetic. Also, anesthesiologists are accustomed to adjusting inspired anesthetic concentrations. The selection of anesthetic dose according to MAC fraction represents a new element.

When we began the study, we generally selected 1.3 MAC as the proper anesthetic concentration for all our patients. In 3 of our first 12 patients this dose was unacceptably large, and the patients became hypotensive even though the measured anesthetic concentration was at or below the concentration we had selected. In 3 other patients hypotension developed while the concentration of anesthetic was higher than that desired. For the remaining 18 patients in the study, we generally used less than 1.3 MAC in order to avoid overdosing less robust patients and to allow an increased margin for error since we had observed that the measured concentration of anesthetic administered might considerably exceed the desired concentration.

The O_2 analyzer presents another problem. While these devices provide an extra margin of safety when a semiclosed system is used, an O_2 analyzer is *required* when N_2O is used in a closed system since the model cannot predict N_2O uptake with sufficient accuracy to avoid hypoxia. We feel that this dependence on an electronic aid is a disadvantage.

Based on our experience with the square root of time model, we wished to develop a simpler method for closed system anesthesia. We sought a technic which would require no equipment other than a standard anesthesia machine, and which would not depend on any new theoretical framework. We felt that many practitioners could readily try such a technic and become familiar with closed system anesthesia.

Examining the protocols from the first group of cases, we realized that after 15 to 25 minutes the rates of administration of anesthetic vapor remained virtually constant and were quite similar in all patients. Feingold has described "coasting" at the end of an anesthetic by closing the system and turning off the flow of the major agent.[19] This sufficiently slows emergence to provide about 15 minutes of anesthesia after 1 hour of halothane or enflurane administration.

We thought that "coasting" could be extended by administering a small amount of vapor to the system. We began anesthesia with a semiclosed system in order to obtain the required concentration of anesthetic in the circuit. While this can be done in a closed system, the semiclosed approach is more familiar to today's anesthesiologists. Once induction was achieved, we felt that anesthetic concentration could be reasonably well maintained for 45 to 60 minutes if we closed the system and discontinued N_2O administration. We arbitrarily selected halothane for this series, and administered 12.5 ml/min of vapor since that appeared representative of values which we actually delivered for the patients in the first part of the study.

What is the margin of safety for this system? When a patient is actually taking up 12.5 ml/min of vapor and 12.5 ml/min is added to the circuit, anesthetic concentration will remain unchanged. However, if a patient were actually taking up twice the amount delivered, how fast would anesthetic concentration decrease? We assume that the patient plus the anesthetic distribution circuit contain approximately 400 ml of halothane when the system is closed and that the patient is taking up 12.5 ml/min more than is being added from the anesthesia machine. If the rate of anesthesia uptake by the patient remained constant, it would take just over 15 minutes for the anesthetic concentration within the breathing circuit to fall to half of its initial value. In fact the concentration would not fall this rapidly, since when the patient's uptake exceeded supply and the concentration began to fall, the rate of uptake would also begin to fall. This simple example demonstrates that anesthetic concentrations within the breathing circuit change slowly and should afford the clinician ample time to recognize clinical consequences.

We can also look at the opposite case, where a patient is taking up only 6.25 ml/min of halothane although we are adding 12.5 ml/min to the system. Therefore an

extra 6.25 ml will be added to the circuit each minute. In this case it would take approximately 30 minutes to double the concentration of anesthetic within the circuit even if uptake continued at the same rate while the concentration was rising. In fact, anesthetic uptake would increase as the circuit concentration rose. Again even the approximate argument, which makes the system appear worse than it actually is, indicates a long time for concentration changes to occur, so that a clinician would have ample opportunity to change the rate of vapor administration.

We had still to resolve the problem of reliance on an O_2 analyzer. We considered what would happen if N_2O administration were discontinued when the system was closed. In our first 30 cases we observed that a N_2O flow rate of between 50 and 100 ml/min was required after the initial 10 to 15 minutes of each anesthetic. We therefore anticipated that if the N_2O flow were discontinued after 10 or 15 minutes of anesthesia and the system were closed, between 30 and 60 minutes would be required to wash N_2O out of the system, assuming an approximately 6-litre gas space. This implies that there would be no hypoxia. Rather, O_2 concentration would always rise.

Therefore, we felt that beginning an anesthetic with a semiclosed system and converting to a closed system had none of the original drawbacks and would keep the system closed 75 percent of the time. A compromise is effected, however, since the total anesthetic dose will vary as N_2O is washed in and out of the system. While this alteration of total anesthetic dose might be expected to pose a clinical problem, none was observed.

We further expected that the technic could be extended for longer procedures. After 45 minutes of closed system anesthesia, the system could be opened and run for 15 minutes with a 5 L/min total flow with 60 percent N_2O and any desired halothane concentration. After this the system could be closed again.

When the closed system is employed three-fourths of the time, each hour will require only one-third of the halothane employed during 1 hour with a 5 L/min total flow and 1 percent halothane. At current prices, this represents a saving of $650 for 1000 such cases considering halothane alone.

One additional comment must be made. To ensure that hypoxia does not occur, volume of gas within the anesthesia circuit must not be allowed to decrease. To prevent this, the system is closed just before the inspiratory phase of respiration. The anesthesia bag is half full when the circuit is closed. Therefore, the system volume can only expand, hastening the rise of O_2 concentration in inspired gas.

What is the significance of our results? We have not presented any statistical analysis. Our study has described our experience with 2 methods for the administration of potent anesthetics in the closed system. We must consider whether either of these technics is reasonable and safe. As we mentioned above, there are some problems associated with the square root of time model. Further, fig 1 shows that when the model was rigidly applied, the average anesthetic concentrations were near those expected; however, there was considerable variability among patients. The variability diminished with time. We felt that the effort of employing the square root of time method would not be justified if a simpler technic would yield similar results.

Figure 2 shows the results of our compromise approach. Average values were near those expected, but there was variability. An analysis of variance could be used to assess the probability that values obtained at different times are essentially the same. However, we do not believe that p values will help the clinician decide if either of the technics described is reasonable and safe. Each clinician must determine that from the description of the technics and the data. We believe that both technics are safe; that the compromise technic is vastly easier to learn and introduce into practice; and that the observed variation among patients mandates vigilance.

In the usual clinical setting, we close the system and administer 12.5 ml/min of halothane. That flow rate is modified as the patient's condition dictates. The anesthesiologist's careful monitoring of the patient, not a mathematical construct, determines the anesthetic course.

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The authors wish to thank Dr. Harry Lowe for teaching them closed system technics and Dr. Helmut F. Cascorbi for continuing guidance and help in preparing the manuscript.

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Current concepts of the etiology, pathophysiology, clinical presentation, prevention, and therapy of respiratory aspiration of stomach contents are presented and discussed. The consequences of aspiration are varied, depending on the amount and distribution of the aspirate, its pH, and the presence or absence of food, particulate matter, and bacteria. Because multiple factors are involved, aspiration of stomach contents can lead to several syndromes of pulmonary injury. The pathophysiology and therapy of each syndrome is reviewed. There are no conclusive clinical or experimental data on which to base the use of corticosteroids in aspiration pneumonia. *(Wynne JW, Modell JH: Respiratory aspiration of stomach contents. Ann Intern Med 87:466-474, 1977)* (See also *Stewardson RH, Nyhus LM: Pulmonary aspiration: An update. Arch Surg 112:1192-1197, 1977)*

Procaine, Lidocaine, and Ketamine Inhibit Histamine-Induced Contracture of Guinea Pig Tracheal Muscle in Vitro

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In vitro experiments using guinea pig tracheal smooth muscle were performed to compare the relaxant properties of procaine, lidocaine, and ketamine following contracture induced by histamine. Procaine produced a spasmolytic effect in a dose-related manner. In the doses tested, relaxation induced by procaine was more pronounced than that produced by either lidocaine or ketamine, although the latter 2 drugs also had a significant spasmolytic effect.

Key Words — ANESTHETICS, local, procaine. ANESTHETICS, local, lidocaine. ANESTHETICS, intravenous, ketamine. LUNG, trachea.

It is quite common in anesthesia practice to use lidocaine topically on the larynx and trachea or IV to suppress the lightly anesthetized patient's reaction to endotracheal intubation manifested by coughing and bronchial spasm. Previous authors have suggested that the suppression of coughing and bronchospasm in this way is central in origin.[1]

It is also common in anesthesia to use ketamine for induction and/or treatment of asthmatic patients.[2]

The purpose of this study was to determine whether lidocaine, ketamine and procaine have spasmolytic effects on tracheal muscle. This was done in vitro using guinea pig tracheal muscle and doses of drugs comparable to those used clinically. The guinea pig tracheal muscle was chosen because of its similarity in pharmacological response to human bronchiolar tissue.[3]

MATERIALS AND METHODS

Guinea pigs weighing between 300 and 500 gm were stunned by a blow on the back of the head and the tracheae removed. After cleaning the tracheae of attached tissues, 6 rings were isolated and attached in a chain pattern according to the method of Castillo and DeBeer.[4] The tracheal chain was suspended in a 10-mm-capacity tissue bath between a fixed hook and a force-displacement (Statham FT03) transducer. Activity was recorded on a multichannel Beckman recorder. The perfusion fluid was Krebs solution, which was constantly bubbled with a mixture of 95 percent O_2 and 5 percent CO_2 at 37° C.

Histamine hydrochloride in the dose of 18 μg/ml (equivalent to 30 μg histamine dihydrogen phosphate) was used as previously described[5] to induce muscle contracture.

After reaching steady state, the dose of the drugs being tested was added to the bath and the amount of relaxation noted over 5 to 10 minutes until a steady state was reached. The specimen was then washed and another dose of the drug added to the bath.

The initial concentration of the drugs tested was calculated on the basis of a clinically administered dose being diluted in the 14 L of extracellular fluid of a 70-kg man (20 percent body weight). Therefore, procaine at a 20 μg/ml concentration in the

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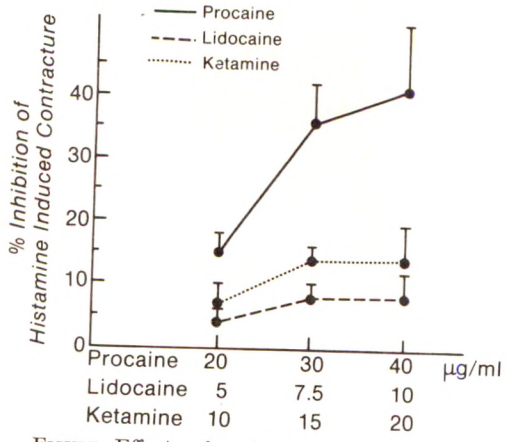


FIGURE. Effects of various concentrations of procaine, lidocaine, and ketamine on histamine-induced contracture of guinea pig tracheal muscle in vitro

bath would correspond to 280 mg given IV. For lidocaine, a 5 µg/ml concentration would be equivalent to 70 mg; and for ketamine, 10 µg/ml would correspond to 140 mg. Consecutive doses tested were 1.5 and 2 times the initial dose of each drug. The number of preparations for each drug was 6 to 9.

RESULTS

Procaine, lidocaine, and ketamine in all concentrations tested produced a statistically significant relaxation of histamine-induced contracture (figure).

There was no dose-related response to any of the doses of lidocaine or ketamine used, but procaine 20 and 40 µg/ml produced a statistically significant inhibition of the histamine-induced contracture of the guinea pig tracheal muscle. However, when comparing drugs at the middle and high doses, there was a statistically significant difference between procaine and either lidocaine or ketamine. There was no significant difference between lidocaine and ketamine at any of the doses.

DISCUSSION

It was shown in this in vitro study that procaine produces a dose-related, statistically significant inhibition of histamine-induced contracture of the guinea pig tracheal muscle. This antagonism of histamine-induced spasm could be due partly to a weak antihistaminic property of procaine. Zipf and Dittman[6] found that local anesthetics depress contraction of smooth muscle strips in vitro, indicating a direct effect, and that this property was unrelated to local anesthetic potency. This concept is supported by the results of this study; procaine is a more potent spasmolytic agent than lidocaine.

In addition to direct effects as studied in the present experiment, IV administered lidocaine suppresses cough reflex and/or prevents spasm of bronchial musculature by a central action of the drug.[1] Weiss et al[7] studied the effects of lidocaine on guinea pig tracheal muscle in vitro and found it effective in reversing or antagonizing the action of various smooth muscle agonists, which they attributed to the stabilizing action of lidocaine on the smooth muscle cell. It should be emphasized, however, that Weiss et al used much higher concentrations of lidocaine than were used in this study. As the concentrations tested in this study were comparable to the clinical range, it can be assumed that in the clinical dose range the main effect of lidocaine on the tracheal musculature is of central origin.

Ketamine, as mentioned above, has been successfully used in relieving bronchial asthma and in the induction of anesthesia in asthmatic patients.[2] The mechanism for this action has been ascribed in part to direct depression of bronchial smooth muscle and in part to elevated blood levels of catecholamines secondary to ketamine administration. Lundy et al[8] found, in in vitro experiments on guinea pig tracheal muscles, that ketamine in the clinical dose range exerts a dose-dependent relaxant effect. Our results showed a significant spasmolytic effect for ketamine but with no significant difference between the 3 doses of the drug. The greater degree of relaxation reported by Lundy et al could be attributed to the stimulating agent (carbachol) used in that study. Even though there was a modest relaxing effect from ketamine in our study, we concur with the conclusions drawn by Lundy et al that this property of ketamine potentiates its other beneficial actions on bronchoconstriction, including increased blood levels of epinephrine, which also produce relaxation of bronchial smooth muscle.

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To determine which preoperative factors might affect the development of cardiac complications after major noncardiac operations, 1001 patients (> age 40) were studied. Nine independent significant correlates of life-threatening and fatal complications were identified: preoperative 3rd heart sound or jugular venous distention; myocardial infarction in the preceding 6 months; more than 5 premature ventricular contractions per minute documented at any time before operation; rhythm other than sinus or presence of premature atrial contractions on preoperative ECG; age over 70 years; intraperitoneal, intrathoracic, or aortic operation; emergency operation; important valvular aortic stenosis; and poor general medical condition. Patients could be separated into 4 classes of significantly different risk. Ten of the 19 postoperative cardiac fatalities occurred in the 18 patients at highest risk. If validated by prospective application, the multifactorial index may allow preoperative estimation of cardiac risk independent of direct surgical risk. *(Goldman L, Caldera DL, Nussbaum SR, et al: Multifactorial index of cardiac risk in noncardiac surgical procedures. New Engl J Med 297:845-850, 1977)*

Chest Physiotherapy: The Effect on Arterial Oxygenation

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A prospective study of 47 patients during mechanical ventilation with positive end-expiratory pressure was undertaken to evaluate changes in Pa_{O_2} following chest physiotherapy. In contrast to other studies, we found no significant change in Pa_{O_2} following chest physiotherapy ($p>0.05$). Different technics for physiotherapy and ventilation may have accounted for the absence of hypoxemia reported by others. Possible reasons for failure to improve Pa_{O_2} were suggested. Chest X-ray before and within 24 hours of physiotherapy showed improvement in 68 percent of patients. Chest physiotherapy was most effective in the treatment of unilobar densities and produced dramatic improvement in atelectasis of acute onset.

Key Words—LUNGS, chest physiotherapy. OXYGEN, Pa_{O_2} and chest physiotherapy.

THE management of patients during prolonged mechanical ventilation and immobilization includes adequate humidification and removal of tracheobronchial secretions. Despite this, lung secretions frequently accumulate beyond the reach of suction catheters and prove unresponsive to simple postural drainage.

In the presence of this problem, we have since 1973 replaced rigid bronchoscopy by chest physiotherapy as the first choice in management. Reports of hypoxemia following chest physiotherapy[2-4] prompted us to undertake this prospective study of the effects of chest physiotherapy on arterial oxygenation.

CLINICAL MATERIAL

Over the years 1973 to 1975, 857 (37 percent) of 2,315 patients admitted to a 12-bed Intensive Care Unit situated at the Maryland Institute for Emergency Medicine (M.I.E.M.) were treated with chest physiotherapy.

We studied 47 patients. The criteria for patient selection were use of mechanical ventilation with positive end-expiratory pressure (PEEP) and the presence of an indwelling arterial catheter. The indications for mechanical ventilation were chest injury in 21 patients, head injury in 13, sepsis in 8, and spinal cord transection in 5. PEEP (5 to 10 cm H_2O) was applied prophylactically as described elsewhere.[1] Thirty-nine of the patients with a mean age of 36 years had trauma. Patients without trauma were older (mean age 64 years) and often suffered from more pathologic conditions than did patients with trauma.

The indications for chest physiotherapy included the presence of audible secretions in the chest due to retained secretions and deterioration of arterial blood gases in association with chest X-ray changes showing atelectasis, pneumonia, or lung contusion.

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METHOD

Chest physiotherapy consists of 4 components: (1) postural drainage, which requires that the patient be placed either in the head-down or head-up position or turned on to the right or left sides with the affected lobe uppermost; (2) external chest compression either by percussion (intermittent clapping of the hands on the chest) or by vibration (intermittent pressure applied with the hands on the chest, coupled with vibration of the chest wall and underlying lung during expiration); (3) encouragement of coughing; and (4) in the intubated patient, tracheobronchial suction to remove secretions mobilized by the above maneuvers.

The 47 patients studied had been ventilated for at least 6 hours prior to the study with an Engstrom 300 ventilator with PEEP of 5 to 10 cm H_2O. Morphine sulfate, fentanyl, or diazepam was given as necessary for sedation. No patients received muscle relaxants.

Arterial blood samples were drawn in all cases with the patient in the supine position immediately prior to physiotherapy, immediately upon completion of physiotherapy, and at half-hour intervals for 2 hours thereafter. Blood samples were placed on ice and analyzed with an Instrumentation Laboratories, Inc., Patient Blood Gas Analyzer (Model No. 313).

The mean duration of treatment was 51 minutes (range 23 to 110 minutes). All patients were examined clinically before and after chest physiotherapy and all had daily chest X-rays. Changes in chest X-ray findings were evaluated by a staff radiologist.

This study was approved by the M.I.E.M. Research Committee and the Human Volunteers Research Committee of the University of Maryland Hospital.

RESULTS

Arterial Oxygenation—The inspired O_2 concentration (mean 42 percent, range 28 to 61 percent), minute volume (mean 14.9 L/min, range 7.75 to 21 L/min), and ventilator settings were kept constant during the period of study.

The mean and SD of Pao_2 values of the 47 patients are shown in fig 1. In a paired *t*-test there was no difference between Pao_2 before physiotherapy and any of the Pao_2 levels after physiotherapy ($p>0.05$). There was also no significant difference in Pao_2 changes between patients with and without trauma ($p>0.05$).

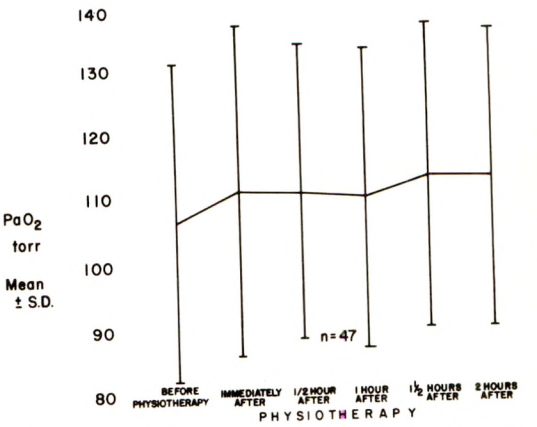


FIG 1. Arterial oxygen tension levels (mean ± SD) before and after chest physiotherapy

Twenty-six patients were in the head down position for physiotherapy. There was no significant difference in Pao_2 levels after treatment ($p>0.05$) in these patients (mean Pao_2 109 ± SD 25.6 torr) and patients in the head up, supine, or lateral positions during chest physiotherapy (mean Pao_2 116 ± SD 22.4 torr).

Clinical and Radiological Findings—On auscultation of the affected lung after physiotherapy, improvement was noted in all 47 cases. Chest X-ray improvement was seen in 68 percent (32 of 47) following treatment. Unilobar densities (27 of 47) were improved in 74 percent of patients. Multilobar densities were seen in 20 of 47 cases and showed improvement in 60 percent (12 of 20) following chest physiotherapy.

DISCUSSION

The lack of significant improvement or decrease in Pao_2 levels after physiotherapy in these 47 patients was in contrast to previously published reports.[2-4] We employed a slightly different physiotherapy technic than in previous studies, since we did not use the "bag squeezing" method described by others.[5] In this method the patient is disconnected from the ventilator and the lungs are hyperinflated with a 4 to 5 L bag while physiotherapy is applied to the affected lung during expiration. In our study, physical therapy was carried out while the patient remained connected to the ventilator, which was only disconnected during tracheal suctioning.

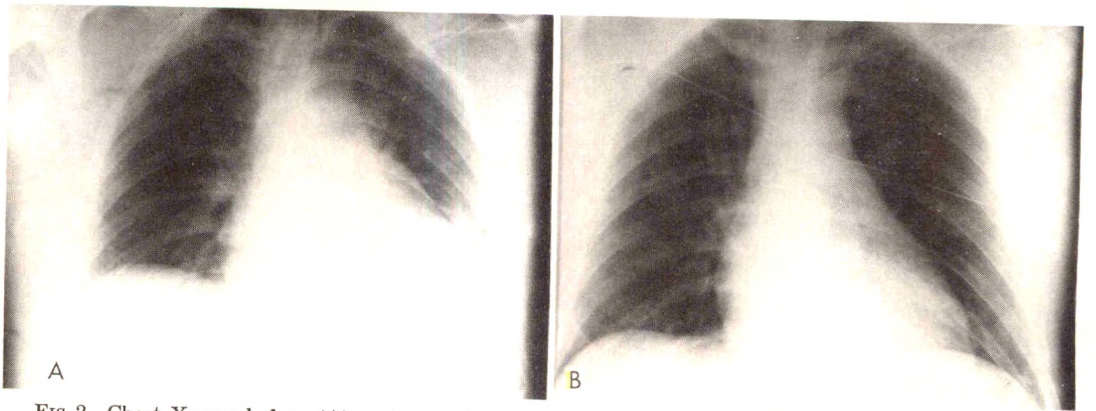


FIG 2. Chest X-rays before (A) and immediately after (B) chest physiotherapy in a patient with acute atelectasis

All patients were ventilated with PEEP (5 to 10 cm H_2O). This is known to prevent small-airways closure[6] and may allow better drainage of secretions. Differing technics for physiotherapy and ventilation may account for our failure to observe the decrease in Pao_2 reported by others. Why Pao_2 values did not show significant increases despite clinical and radiological improvement is not apparent. Endotracheal suction[7] and ventilation perfusion changes may have been factors.

Following chest physiotherapy, 68 percent (32 of 47) of the patients showed evidence of improvement by chest X-ray. This is similar to the 67 percent improvement (47 of 70) in chest X-ray appearance reported by Lindholm et al[8] when fiberoptic bronchoscopy was used to clear secretions. Chest physiotherapy was most effective in unilobar pathology, producing a dramatic improvement in atelectasis of acute onset (fig 2A and B). Chest physiotherapy offers a less invasive method than bronchoscopy of clearing retained secretions during prolonged mechanical ventilation.

ACKNOWLEDGMENT

We are grateful to R. Ayella, MD, Professor of Radiology, for reading the chest X-rays and to the physiotherapists in the Department of Rehabilitation Medicine for their cooperative effort.

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Central Vagal Control of Fentanyl-Induced Bradycardia During Halothane Anesthesia

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Six mongrel dogs were used to investigate the mechanism of action of fentanyl-induced bradycardia. With controlled acid-base balance and temperature, and under 1.0 to 1.2 percent end-tidal halothane anesthesia, 5 and 10 μg/kg of IV fentanyl citrate were given sequentially 1 hour apart and heart rate (HR) followed for 60 minutes. A dose-related depression of HR followed both injections. One week later the same dogs were studied similarly, except that bilateral cervical vagotomies were performed before fentanyl was given. The decrease in HR was at most 10 percent of the decrease in HR observed in the innervated dogs. Serum fentanyl levels were comparable. The data indicate the majority of the chronotropic action of fentanyl involves vagal efferent impulses from the central nervous system.

Key Words — ANESTHETICS, intravenous, fentanyl. ANALGESICS, narcotic, fentanyl.

FENTANYL citrate is a well-known, fast-acting narcotic used extensively in anesthesia. It causes bradycardia in humans[1,2] and animals,[3] which is most pronounced when administered to anesthetized subjects. This effect may be reversed by the narcotic antagonist naloxone[4] or attenuated by atropine.[3] The purpose of this study was to determine whether the bradycardia has a peripheral or central neurogenic origin, or whether it is the result of direct cardiac depression.

METHOD

Six mongrel dogs of either sex (average weight 21.6 ± 0.9 kg) were anesthetized with halothane-O_2, their tracheas were intubated, and they were ventilated with a piston-type respirator. A 20-g Teflon 2.5-in. catheter was placed percutaneously in the femoral artery for arterial blood gas analysis and measurement of mean arterial blood pressure on a Statham P-23db transducer. Lead II ECG was recorded and a peripheral venous line started. Ventilation was adjusted to provide a $Paco_2$ of 28 to 35 torr and the end-tidal halothane concentration, measured on a Beckman LB-2 analyzer, was held at 1.0 to 1.2 percent. Blood gas analysis was performed on an IL 113 machine and ECG and mean arterial pressure ($\overline{AP}$) recorded on a calibrated oscillograph at 10 mm/sec. Distal esophageal temperature was measured by a thermistor probe and kept constant by heating lamps and circulating blanket. Heart rate (HR) was obtained from the ECG as the reciprocal of the R-R intervals measured over a 15-second interval and concurrent $\overline{AP}$ was noted.

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After steady state anesthesia and acid-base balance were obtained, baseline heart rate and blood pressure variables were recorded. An IV dose of 5 μg/kg of USP fentanyl citrate was followed by recordings of HR and $\overline{AP}$ at intervals of 0.5, 5, 10, 15, 30, 45, and 60 minutes after injection. Serum concentrations determined by radioimmune assay were obtained at the first 4 data points. At 60 minutes, new control variables were recorded and 10 μg/kg of fentanyl citrate was administered IV. The same variables were measured again at the same intervals, and serum fentanyl levels were measured at all data points.

The dogs recovered from anesthesia, and 1 week later each was studied again in the same fashion except that a bilateral cervical vagotomy was performed before the fentanyl was given.

The technic for measuring fentanyl involves production of rabbit sera antibodies to the fentanyl moeity and subsequent assay of the inhibition of a prepared tritiated fentanyl compound.[5] Sensitivity of this test reaches 0.3 nanograms/ml serum with an accuracy of ± 5 percent at all serum levels. The lowest fentanyl level in our experiment was at least 4 times greater than the limit of sensitivity and all samples were run in duplicate. Compared to fentanyl, the major metabolite of fentanyl—anilino-piperidine—is 100 times attenuated in its binding capacity with the antisera.[6]

The data were analyzed on a Tektronix Model 31 programmable calculator, and statistical significance determined by a standard Student's *t*-test.

RESULTS

Figures 1 and 2 show the effects of fentanyl citrate on HR in both innervated and vagotomized dogs after 5 μg/kg and 10 μg/kg doses. In innervated animals, a time-related depression of HR was observed at both dose levels to a low of 60 percent of control value 10 minutes following the large dose. Statistically significant reductions in rate were evident in innervated animals for 15 minutes after 5 μg/kg and for the entire hour after 10 μg/kg. There was an obvious trend toward dose dependency in the innervated animals between 5 μg/kg and 10 μg/kg and this difference was maintained throughout the time of the experiment (fig 3).

After vagotomy, the same dogs showed little change in HR when fentanyl was given; the lowest point was 96 percent of control, again 10 minutes after the larger dose.

Surgical vagotomy increased the absolute HR significantly in the animals at both dose levels of the drug. Control HR was 89.0 ± 5.6 beats/min (BPM) for 5 μg/kg of fentanyl and 90.3 ± 7.7 BPM for 10 μg/kg. After vagotomy, control HR rose to 127.3 ± 1.6 BPM and 125.7 ± 2.5 BPM respectively.

Fentanyl caused a significant fall in $\overline{AP}$ at both dose levels, and this action of the

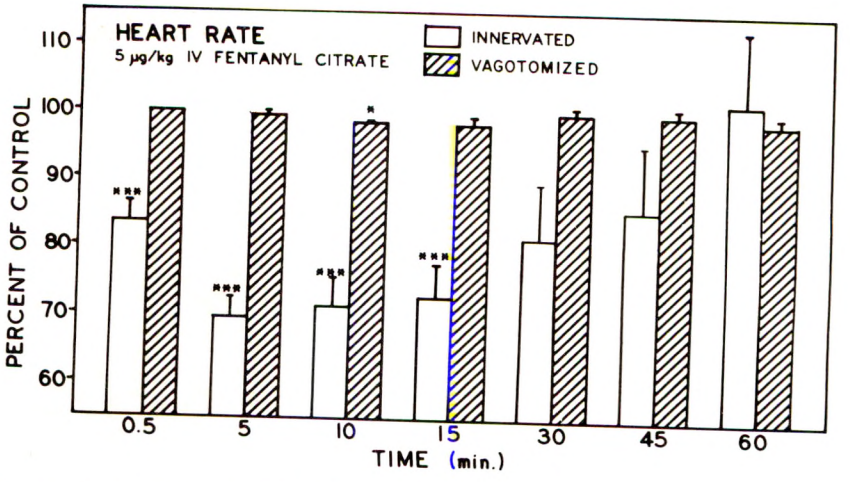


FIG 1. A bar graph of the effect on HR of 5 μg/kg of fentanyl citrate IV is shown over 60 minutes as percent of predrug control HR levels. The arithmetic means ± 1 SEM are plotted for the 6 innervated and surgically vagotomized dogs.
* = significantly different ($p<0.05$) from control.
*** = significantly different ($p<0.001$) from control.

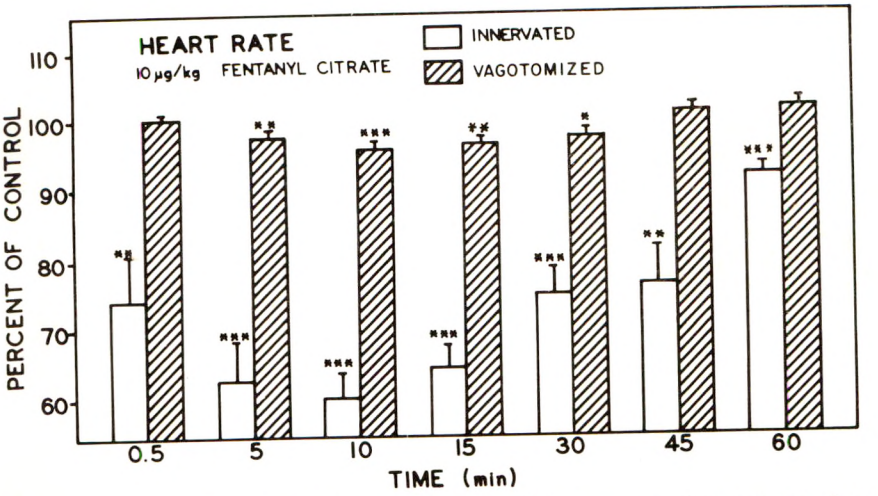


FIG 2. Response of HR to 10 μg/kg fentanyl citrate IV in 6 dogs expressed as percent of control HR values obtained immediately prior to administration. The arithmetic means ± 1 SEM are plotted as in fig 1.
* = significantly different ($p<0.05$) from control.
** = significantly different ($p<0.01$) from control.
*** = significantly different ($p<0.001$) from control.

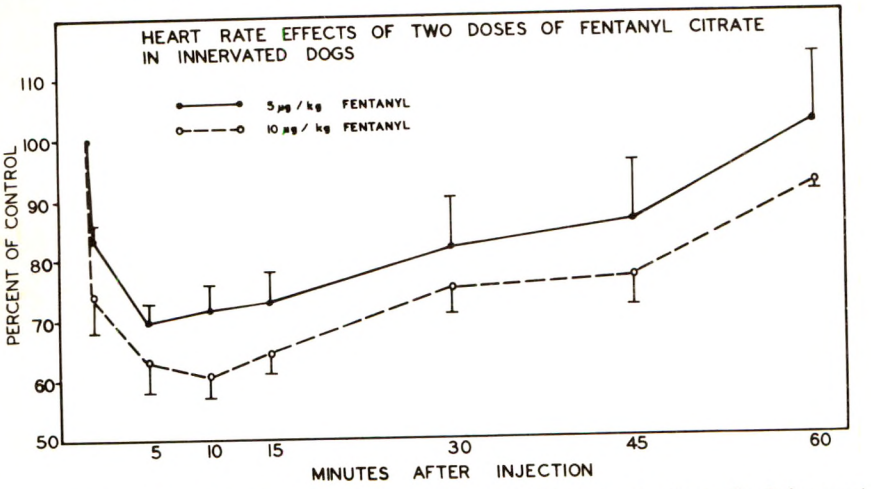


FIG 3. A comparison of HR depression by the 2 doses of IV fentanyl citrate in 6 innervated dogs. The data were collected at 0.5, 5, 10, 15, 30, 45, and 60 minutes after injection and each point is represented as the mean percent of predrug control ± 1 SEM.

drug was not prevented by vagotomy (table 1). No dose dependency was obvious in $\overline{AP}$ changes.

Serial serum concentrations of fentanyl followed a typical redistribution curve after the larger dose of fentanyl (fig 4). Although serum concentrations were consistently less in the vagotomized animals at both dose levels (table 2), a statistically significant difference between the innervated and vagotomized dogs occurred only at 15 minutes into the 10 μg/kg run.

A summary of anesthetic concentrations, acid-base balance, and rectal temperature values is listed in table 3.

DISCUSSION

Using amounts of fentanyl somewhat greater than our larger dose (10 μg/kg), other investigators found marked HR slowing in dogs with intact vagi. Freye[4] observed a 50-percent reduction with 40 μg/kg while Eisele et al[3] noted a 47-percent decrease in HR following a cumulative dose of 20 μg/kg in dogs not treated with atropine. In our innervated animals we produced a maximum slowing of 40 percent with 10 μg/kg

TABLE 1
$\overline{AP}$ Changes at Intervals (in Minutes) After Fentanyl Injection

	0.5	5	10	15	30	45	60
Innervated							
5 μg/kg	96.7	77.0	70.8	82.1†	91.7	100.9	111.4
± SEM	±2.9	±4.4	±13.8	±5.4	±4.7	±2.7	±6.3
10 μg/kg	98.8	77.3‡	73.0‡	73.3‡	79.6‡	86.3*	92.2
± SEM	±7.0	±4.8	±5.6	±5.5	±3.6	±5.0	±7.4
Vagotomized							
5 μg/kg	99.4	92.5*	80.9†	74.2†	75.2†	78.7*	78.4*
± SEM	±1.8	±3.3	±4.8	±5.7	±7.7	±8.3	±8.0
10 μg/kg	101.0	95.3	92.9	86.7‡	86.9*	95.5	102.8
± SEM	±1.9	±3.6	±4.0	±2.8	±5.8	±6.3	±5.2

Mean arterial blood pressure effects of the 2 doses of fentanyl citrate (5 μg/kg and 10 μg/kg) in 6 innervated and vagotomized dogs measured at stated intervals after administration are listed. The data are the arithmetic mean ± 1 SEM expressed as a percent of predrug control values. * = significantly different from control ($p<0.05$). † = significantly different from control ($p<0.01$). ‡ = significantly different from control ($p<0.001$).

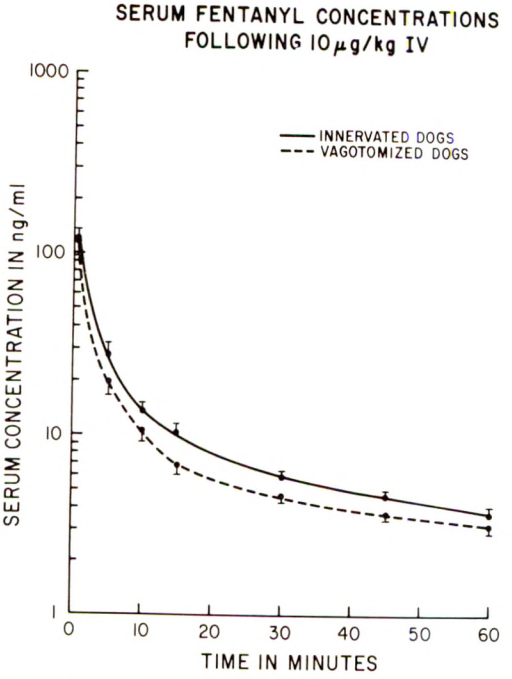


FIG 4. Serum fentanyl levels obtained by radioimmune assay in 6 innervated and vagotomized dogs as a function of time following an IV injection of 10 μg/kg. The collection points are similar to the measurement times in fig 3. The mean concentrations ± 1 SEM are expressed in nanograms/ml of sampled serum on a logarithmic scale. The best-fit connecting lines are hand drawn.

fentanyl citrate, so an apparent dose-related depression of HR occurs on the basis of the combined data in these studies.

Marta et al[7] proposed that the bradycardic mechanism of Innovar® (a drug which includes fentanyl) could involve (1) excitation of the central vagal centers; (2) attenuation of the sympathetic nervous system; (3) depression of the myocardium; or (4) direct peripheral vagal stimulation. At the larger dose in surgically vagotomized dogs, we found a maximum reduction in HR of 4 percent, or approximately one-tenth the fall that occurred in innervated animals. Consequently, in our study at least 90 percent of the mechanism for fentanyl-induced bradycardia originates in central vagal control centers and only about 10 percent elsewhere. In Eisele's series,[3] 1 mg/kg of atropine sulfate was used in the 2nd part of the experiment to block the vagus peripherally. Some slowing of HR (12 percent) still occurred after subsequent administration of fentanyl, but there was no change in myocardial inotropy. Similarly, Freye's[4] animals exhibited no direct myocardial depression following large doses of fentanyl citrate. The slowing of HR produced by fentanyl which is not under central vagal control may be the result of attenuation of sympathetic chronotropic action.

The effect on HR of interaction between fentanyl and the halothane used in this study is unclear. Vatner and Smith's[8] study of the cardiovascular effects of halothane in dogs showed that during 1 percent end-tidal halothane anesthesia (comparable to our animals' anesthetic level), HR rose significantly from awake controls and remained 10 percent elevated 90 minutes after anes-

TABLE 2
Serum Concentrations (ng/ml) at Intervals (Minutes) After Fentanyl Injection

	0.5	5	10	15	30	45	60
			5 μg/kg				
Innervated	68.9 ± 15.4	11.7 ± 1.8	6.2 ± 0.9	4.7 ± 0.7	——	——	1.8 ± 0.5
Vagotomized	50.1 ± 6.0	8.8 ± 1.4	4.4 ± 0.6	3.1 ± 0.4	——	——	1.2 ± 0.1
			10 μg/kg				
Innervated	120.1 ± 14.1	27.3 ± 4.5	13.3 ± 1.6	10.1 ± 1.4	5.8 ± 0.6	4.6 ± 0.4	3.7 ± 0.4
Vagotomized	118.2 ± 21.9	19.8 ± 3.3	10.5 ± 1.1	6.7 ± 0.6*	4.6 ± 0.2	3.7 ± 0.2	3.1 ± 0.2

Each data point is the mean value ± 1 SEM for all 6 animals at the 7 collection times. No measurements were made 30 or 45 minutes after the 5 μg/kg dose. There was a statistically significant difference between the innervated and vagotomized dogs 15 minutes after the 10 μg/kg dose (* = $p<0.05$).

TABLE 3
End-Tidal Halothane Concentration in Innervated and Vagotomized Dogs

	ET Hal (vol %)	pH_a	$Paco_2$ (torr)	BE (mEq/L)	Temp (°C)
Innervated					
Beginning	1.08 ± 0.02	7.46 ± 0.08	29.3 ± 1.4	−1.8 ± 1.0	38.7 ± 0.3
Midpoint	1.09 ± 0.03	7.46 ± 0.01	31.0 ± 2.0	−1.5 ± 0.6	38.4 ± 0.1
End	1.08 ± 0.03	7.42 ± 0.02*	35.5 ± 1.9*	−1.3 ± 0.8	38.5 ± 0.1
Vagotomized					
Beginning	1.10 ± 0.01	7.43 ± 0.01	29.7 ± 1.5	−3.3 ± 1.0	39.0 ± 0.4
Midpoint	1.09 ± 0.03	7.40 ± 0.02	33.7 ± 2.5	−3.7 ± 0.6	38.5 ± 0.2
End	1.09 ± 0.02	7.41 ± 0.02	35.1 ± 2.3	−2.0 ± 0.5	38.7 ± 0.2

Values for end-tidal halothane concentration (ET Hal), arterial blood pH, arterial partial pressure of CO_2, calculated base excess (BE), and temperature are compared in both innervated and vagotomized dogs at 3 times in the experimental protocol. "Beginning" is immediately before any fentanyl was given; "midpoint" is before the larger dose was administered; "end" is 60 minutes after the larger dose. There were statistically significant differences in pH_a and $Paco_2$ values of the innervated dogs at the beginning and at the end (* = $p<0.05$).

thesia began. They postulated that the change in HR was probably a reflex in response to myocardial depression, lowered cardiac output, and blood flow redistribution caused by halothane. In all our dogs the sympathetic innervation was intact, and a reflex increase in HR caused by halothane could have been attenuated subsequently by fentanyl. This mechanism would account for the 10-percent decrease in HR seen in the vagotomized animals.

The cause for the fall in $\overline{AP}$ after both doses of fentanyl was not investigated since we did not measure cardiac output or specific regional blood flows. However, there was substantially less fall in $\overline{AP}$ after the larger dose of fentanyl in the vagotomized than in the innervated animals. In vagotomized dogs the increased HR could have maintained a higher cardiac output as a method for supporting the $\overline{AP}$. Studies by Liu et al[9] have shown that fentanyl reduces $\overline{AP}$ by changes in cardiac output and calculated peripheral resistance, although the decreases occurred at a higher dose level in their work. Moreover, their animals were lightly anesthetized with thiopental and succinylcholine while ours were under baseline halothane. Again, potential synergistic depressive effects of halothane must be considered.

Serum fentanyl concentrations plotted against time suggest a difference between the innervated and vagotomized animals at both dose levels although statistical significance was reached only 15 minutes after the larger dose (table 3). The slope of the redistribution curve is dependent on the cardiac

output and the volume into which redistribution occurs. Since each dog served as his own control and presumably contained the same redistribution volume, the discriminating variable between the innervated and vagotomized animals was cardiac output. Again it is reasonable to assume that the increased HR with vagotomy could account for a change in cardiac output and the slight lowering of serum concentrations in the vagotomized dogs. However, the difference was mostly insignificant and it can be assumed that both series of dogs had close to the same concentration of drug at their appropriate receptor sites.

In summary, our data, obtained under controlled acid-base, anesthetic, and temperature conditions, demonstrate that the major part of negative chronotropic action of fentanyl is vagally transmitted and probably stems from central vagal centers in the dogs.

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Acute fulminating pulmonary edema developed in 3 patients after acute airway obstruction secondary to tumor, strangulation, and interrupted hanging (1 case each). The common etiologic factor was vigorous inspiratory effort against a totally obstructed upper airway. Acute pulmonary edema followed the event in minutes to hours and required ventilatory assistance to maintain oxygenation. All patients eventually responded to fluid restriction, diuretics, and steroids. The pathogenesis is presumed to be related to alveolar and capillary damage induced by the negative pressure generated by attempting to inspire against the obstructed upper airway. *(Oswalt CE, Gates GA, Holmstrom FMG: Pulmonary edema as a complication of acute airway obstruction. JAMA 238:1833-1835, 1977)*

Correlation of Oxygen Uptake and Cardiovascular Dynamics During N_2O-Fentanyl and N_2O-Thiopental Anesthesia in the Dog

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The relationship between changes in whole-body O_2 consumption ($\dot{V}O_2$) and cardiovascular dynamics during changing levels of N_2O-fentanyl and N_2O-thiopental anesthesia was determined in 24 dogs. Dose-dependent reductions in $\dot{V}O_2$, mean blood pressure, and cardiac output occurred with infusion of fentanyl and thiopental. Painful stimuli increased $\dot{V}O_2$ during light anesthesia but not during deeper levels of anesthesia. Deep levels of N_2O-fentanyl and N_2O-thiopental anesthesia may protect the patient with limited cardiac reserve by reducing $\dot{V}O_2$ and preventing increases in $\dot{V}O_2$ caused by painful stimuli.

Key Words—OXYGEN, consumption. ANESTHESIA, depth. ANESTHETICS, gases, nitrous oxide. ANESTHETICS, intravenous, fentanyl. ANESTHETICS, intravenous, thiopental. ANALGESICS, narcotic, fentanyl.

RECENT studies have demonstrated that, in contrast to previous beliefs, the anesthetic state is not necessarily associated with a decrease in whole-body O_2 consumption ($\dot{V}O_2$).[1,2] Indeed, while halothane produces a concentration dependent reduction in $\dot{V}O_2$,[1] diethyl ether anesthesia is associated with an increase in $\dot{V}O_2$.[3] Subsequent investigations[1,4,5] have found that many factors must be considered in predicting $\dot{V}O_2$ changes during anesthesia including premedication, muscle relaxants, body temperature, and degree of muscle activity.

Nitrous oxide-fentanyl and N_2O-thiopental are popular anesthetic technics. However, their influence on $\dot{V}O_2$ is not clearly established. Furthermore, the effect of painful stimuli on $\dot{V}O_2$ during anesthesia with these agents is also unknown. The purposes of this study were to measure $\dot{V}O_2$ during changing levels of N_2O-fentanyl and N_2O-thiopental anesthesia and to establish the relationships, if any, that may exist between alterations in $\dot{V}O_2$ and cardiovascular dynamics during anesthesia with these agents.

METHODS

Twelve unpremedicated mongrel dogs (17 to 25 kg) served as experimental subjects. Each had an infusion of lactated Ringer's solution started in a foreleg vein and was anesthetized with 25 mg/kg of sodium thiopental IV. Following endotracheal intubation, the dogs were mechanically ventilated

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with humidified 50 percent N_2O in O_2 with a volume-limited respirator. Respirations were controlled at a rate of 8 to 15 breaths/min and a tidal volume of 9 to 15 ml/kg in order to maintain the arterial CO_2 partial pressure ($Paco_2$) between 30 to 35 torr. A continuous infusion of thiopental (0.5 mg/kg/min) was started immediately after intubation to maintain basal anesthesia during preparatory procedures and during the control period. Thiopental infusion was stopped in the fentanyl group at the end of the control period. Catheters were placed in the pulmonary artery via the femoral vein and in the aorta through a small groin incision. The pulmonary arterial catheter was used for thermodilution cardiac-output determination. The aortic catheter was used for blood sampling, pressure and heart rate monitoring, and determination of cardiac output utilizing the method of Warner and coworkers after thermodilution calibration.[6]

$\dot{V}O_2$ was measured using an instrument previously described.[7,8] Two feedback control loops, one for O_2 and a second for N_2O, were added to a conventional rebreathing circuit. The O_2 feedback loop consists of an O_2 polarographic sensor, feedback control electronics, and an O_2 pump. Metabolic O_2 removed from the rebreathing circuit during anesthesia is replaced by the O_2 pump, thus maintaining a constant O_2 concentration within the circuit. The 2nd feedback loop contains a volume sensor, control electronics, and a N_2O pump. The N_2O pump maintains a constant circuit volume by adding N_2O to the rebreathing circuit. Comparison of this method with a standard open-circuit method of measuring $\dot{V}O_2$ (gas collection and analysis) has yielded a correlation coefficient of 0.94.[8]

$Paco_2$, arterial pH, and arterial O_2 tension were measured with a Radiometer blood gas machine. Esophageal temperature was determined with a Yellow Spring temperature probe and maintained at 38° C, using warming blankets when necessary.

Following preparatory procedures, control values of heart rate (HR), cardiac output ($\dot{Q}_T$), mean blood pressure ($\overline{BP}$), and $\dot{V}O_2$ were obtained by averaging measurements made every 5 minutes over a 20-minute control period (period A). Following this, 6 of the dogs were given an infusion of 0.005 percent fentanyl citrate IV at a rate of 3.0 μg/kg/min. The other 6 animals received 2.5 percent sodium thiopental IV at a rate of 2.1 mg/kg/min. All variables were recorded every 2 minutes for the next 10 minutes (period B). The infusion rates were then reduced 50 percent and variables remeasured every 2 minutes for the next 20 minutes (period C). Following this, the infusions were stopped and all variables recorded at 5-minute intervals for the ensuing 50 minutes (period D).

An additional 12 dogs were anesthetized and monitored in the same fashion (half receiving similar infusions of fentanyl and half similar infusions of thiopental) as the original animals except each was subjected to 2 minutes of a painful stimulus (tail clamping) between the 2nd and 4th minutes of period B, between the 8th and 10th minutes of period C, and between the 33rd and 35th minutes of period D.

Data points were determined to be statistically different from control using Student's *t*-test and a significance level of $p<0.05$. The correlation between $\dot{V}O_2$ and $\overline{BP}$, HR, and $\dot{Q}_T$ was expressed using the standard correlation coefficient equation.[9] The statistical significance of the change caused by painful stimuli was determined using Student's paired *t*-test, comparing the measurement immediately preceding the tail clamp and the reading taken just before the clamp was removed.

RESULTS

Changes in $\dot{V}O_2$, HR, $\dot{Q}_T$, and $\overline{BP}$ during and after fentanyl and sodium thiopental infusions are summarized in fig 1 to 4. Fentanyl produced a dose-related reduction in all variables measured during the period of rapid drug infusion (period B) but did not

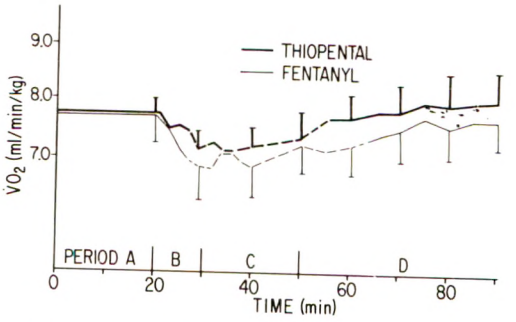


FIG 1. Total-body O_2 consumption (mean ± SE) during a control period with N_2O anesthesia (period A), during increasing depth of anesthesia with N_2O plus fentanyl or thiopental (period B), during a period of constant anesthesia (period C), and during recovery from anesthesia (period D). The dashed line represents values which are statistically different from control values ($p<0.05$).

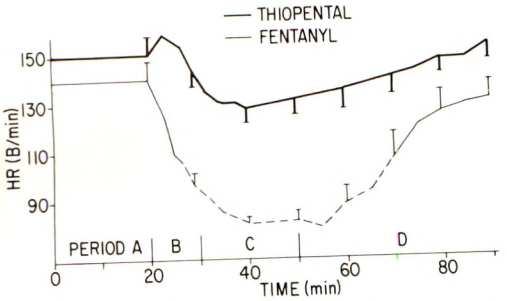


FIG 2. Heart rate (mean ± SE) during a control period with N_2O anesthesia (period A), during increasing depth of anesthesia with N_2O plus fentanyl or thiopental (period B), during a period of constant anesthesia (period C), and during recovery from anesthesia (period D). Dashed lines as in fig 1.

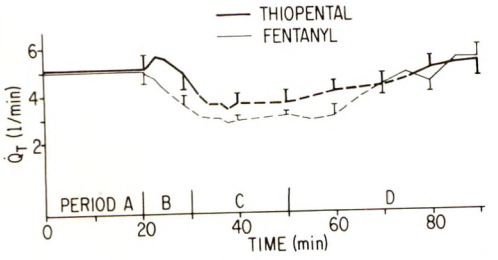


FIG 3. Cardiac output (mean ± SE) during a control period with N_2O anesthesia (period A), during increasing depth of anesthesia with N_2O plus fentanyl or thiopental (period B), during a period of constant anesthesia (period C), and during recovery from anesthesia (period D). Dashed lines as in fig 1.

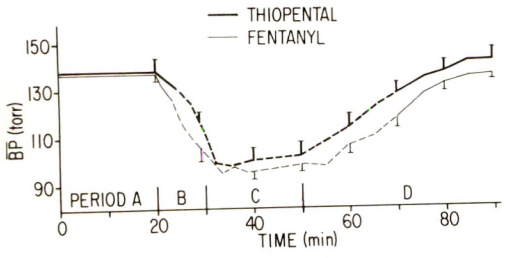


FIG 4. Blood pressure (mean ± SE) during a control period with N_2O anesthesia (period A), during increasing depth of anesthesia with N_2O plus fentanyl or thiopental (period B), during a period of constant anesthesia (period C), and during recovery from anesthesia (period D). Dashed lines as in fig 1.

further influence any of the variables when the infusion rate was decreased 50 percent (period C). Termination of fentanyl (period D) resulted in a gradual return of all variables toward control values. Changes during and after sodium thiopental infusion were similar to those with fentanyl except that HR and $\dot{Q}_T$ were initially slightly increased during period B.

Correlation of $\dot{V}O_2$ changes with those in $\dot{Q}_T$, $\overline{BP}$, and HR during and after fentanyl infusion were high, $r > 0.99$, and $r > 0.93$ in periods B and D, respectively, as shown in table 1. $\dot{V}O_2$ changes were also well correlated with $\overline{BP}$ during periods B and D of the thiopental infusion, $r = 0.89$ and $r = 0.94$, respectively. Correlation of $\dot{V}O_2$ with $\dot{Q}_T$ and HR was lower, $r < 0.31$ and $r < 0.11$, with thiopental infusion during these same periods.

With fentanyl there was a significant rise ($p < 0.05$) in $\dot{V}O_2$ when a tail clamp was given late in period D (fig 5). No change was seen when the clamp was given during periods B or C. There was no significant response to tail clamping at any time during thiopental infusion.

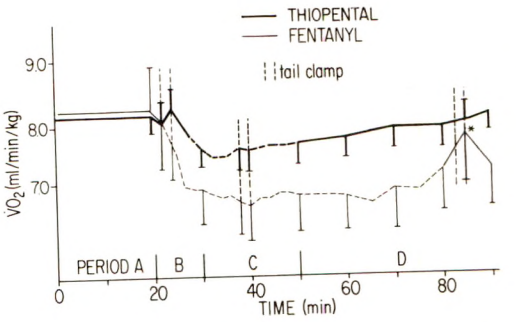


FIG 5. Total-body O_2 consumption (mean ± SE) during a control period (period A), induction of fentanyl and thiopental anesthesia (period B), constant anesthesia (period C), and recovery from anesthesia (period D). A painful stimulus was given during the time bracketed by 2 dashed lines. An * represents a data point significantly different ($p<0.05$) from the value immediately preceding the tail clamp. The dashed record represents values significantly different from control values.

TABLE 1

Coefficients of Correlation Between Changes in Oxygen Consumption and Changes in Cardiovascular Variables

	Period B	Period D
Fentanyl anesthesia		
HR - $\dot{V}O_2$	0.99	0.94
$\dot{Q}_T$ - $\dot{V}O_2$	0.99	0.97
$\overline{BP}$ - $\dot{V}O_2$	0.99	0.93
Thiopental anesthesia		
HR - $\dot{V}O_2$	0.31	0.88
$\dot{Q}_T$ - $\dot{V}O_2$	0.11	0.88
$\overline{BP}$ - $\dot{V}O_2$	0.89	0.94

DISCUSSION

The results of this study demonstrate that infusions of fentanyl or thiopental during N_2O anesthesia result in significant reductions in $\dot{V}O_2$, $\overline{BP}$, and $\dot{Q}_T$ and, with fentanyl but not thiopental, a reduction in HR. Painful stimulation may increase $\dot{V}O_2$ during light levels of anesthesia, ie, early in period B and late in period D but not during a period of deep anesthesia, period C. The data indicate that changes in $\dot{V}O_2$ are highly correlated with simultaneous changes in $\dot{Q}_T$, $\overline{BP}$, and HR during anesthesia with N_2O-fentanyl. With N_2O-thiopental anesthesia there is high correlation between $\dot{V}O_2$ and $\overline{BP}$, $r = 0.89$ and 0.94.

The effect of anesthesia on $\dot{V}O_2$ depends on the anesthetic used; anesthesia itself does not necessarily reduce metabolism.[1,2] If organ function (ie, myocardial work) remains unchanged during anesthesia, metabolism is likely to be unchanged. On the other hand, if organ function is depressed or stimulated, $\dot{V}O_2$ is likely to be similarly altered. In a report investigating the influence of halothane on $\dot{V}O_2$, myocardial O_2 consumption ($M\dot{V}O_2$), and cardiovascular dynamics, Theye[1] found that halothane produced concentration-dependent decreases in $\dot{V}O_2$, $M\dot{V}O_2$, $\dot{Q}_T$, and $\overline{BP}$ in dogs. Using estimates of splanchnic, renal, cerebral, and skeletal muscle $\dot{V}O_2$ and direct measurements of $M\dot{V}O_2$, he demonstrated that almost half of the decrease in $\dot{V}O_2$ during halothane anesthesia was due to reduction in $M\dot{V}O_2$.

While $M\dot{V}O_2$ was not directly measured in our study, calculated changes in $M\dot{V}O_2$ using the relationship derived by Theye[4]—$M\dot{V}O_2 = (\dot{Q}_T \times \overline{BP} \times 0.0144) \times 2.1 + 1.4$—correlated well with simultaneous changes in $\dot{V}O_2$ during all aspects of the investigation (table 2).* Correlation between $\dot{V}O_2$ and $M\dot{V}O_2$ plus high correlations of changes in $\dot{V}O_2$ with those in $\overline{BP}$ and $\dot{Q}_T$, 2 important determinants of myocardial energy expenditure, suggest that changes in $M\dot{V}O_2$ may also be a major source of changes in $\dot{V}O_2$ during N_2O-fentanyl and N_2O-thiopental anesthesia.

TABLE 2

Coefficients of Correlation Between Changes in Oxygen Consumption and Changes in Estimated Myocardial Oxygen Consumption*

	Period B	Period D
Fentanyl anesthesia		
$M\dot{V}O_2 - \dot{V}O_2$	0.96	0.86
Thiopental anesthesia		
$M\dot{V}O_2 - \dot{V}O_2$	0.70	0.89

*Myocardial O_2 consumption estimated from the product of $\dot{Q}_T$ and $\overline{BP}$ as discussed in the text.

Increases in O_2 demand greater than simultaneous increases in blood flow are a mechanism for the production of tissue ischemia and myocardial infarction. Modern anesthesiologists are anesthetizing increasing numbers of patients with coronary artery disease for repair of their diseased coronary arteries as well as for numerous other vascular and nonvascular operations. Nitrous oxide plus morphine, meperidine, or fentanyl is frequently employed for anesthesia in these procedures.[10-12] The data in this study demonstrate that high doses of fentanyl and thiopental significantly reduce whole body $\dot{V}O_2$ and prevent increases in $\dot{V}O_2$ during painful stimuli. Lower doses of fentanyl may be unsuccessful in preventing undesired increases in $M\dot{V}O_2$ and whole body $\dot{V}O_2$ during painful stimuli.

A possible criticism of the study could be the use of thiopental as a basal anesthetic agent during the preparation and control period. Certainly a basal anesthetic in addition to N_2O was needed during this period. Any anesthetic agent would have some effect on the results, and background thiopental surely had an effect on the fentanyl group. In an effort to standardize this effect the same dose of thiopental was used in both the fentanyl and the thiopental groups, thus making it possible to study the differences between fentanyl and thiopental.

*A number of other methods for calculating myocardial O_2 consumption exist. Among them are methods using the arterial blood pressure and heart rate product, the area under the ventricular systolic pressure curve, and the maximal velocity of myocardial isotonic shortening. The method used in our work (cardiac output and mean blood pressure product) was chosen because of the ease of calculation and previous application and verification of accuracy in the anesthetized dog.

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Tension pneumomediastinum producing tracheal compression and obstruction to venous return occurred in an adult patient during prolonged mechanical ventilation. The obstruction was relieved by a mediastinotomy, performed at the bedside through a suprasternal incision. Tension pneumomediastinum is an infrequent but potentially fatal complication of mechanical ventilation in patients of all ages. Mediastinotomy is advocated for the rapid relief of airway and vascular compression. *(Stiegmann GV, Brantigan CO, Hopeman AR: Tension pneumomediastinum. Arch Surg 112:1212-1215, 1977)*

Bupivacaine: A Review of 11,080 Cases

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Bupivacaine (Marcaine®) hydrochloride, a long-acting local anesthetic drug, was used in concentrations of 0.25, 0.5, or 0.75 percent with and without a vasoconstrictor, in amounts ranging from 25 to over 600 mg, for caudal, epidural (peridural), or peripheral nerve block for 11,080 surgical, obstetrical, diagnostic, or therapeutic procedures. Onset of anesthesia occurred in 4 to 10 minutes and maximum anesthesia in 15 to 35 minutes. Concentrations of 0.25, 0.5, and 0.75 percent consistently produced complete sensory anesthesia of the integumentary and musculoskeletal systems. With 0.25 and 0.5 percent, motor blockade ranged from minimal to complete. In intra-abdominal surgery, only 0.75 percent consistently produced profound muscle relaxation. Fifteen systemic toxic reactions occurred, but no untoward sequelae resulted from them. One inadvertent subarachnoid injection of 110 mg resulted in a total spinal block with an uneventful recovery.

Key Words — ANESTHETICS, LOCAL; Bupivacaine. ANESTHETIC TECHNICS, regional.

THIS study summarizes our clinical experiences with bupivacaine (Marcaine) hydrochloride (1-n-butyl-DL-piperidine-2-carboxylic acid-2,6-dimethylanilide hydrochloride), a long-acting local anesthetic drug, in 11,080 regional block procedures performed from 1966 through 1976.[1-11] It documents the following: (1) optimal safe doses (volumes and concentrations) of bupivacaine for caudal, epidural (peridural), and peripheral nerve block; (2) times required for onset of analgesia and for establishment of complete operative anesthesia, as well as duration of both surgical anesthesia and postoperative analgesia; and (3) complications which have occurred while using this drug.

METHOD

The data we collected during the investigation of bupivacaine in the USA (1966 to 1968) were retrieved from computer printouts of the forms required by the Food and Drug Administration when bupivacaine was still an "experimental" drug. During the next four years, when these investigational data were being reviewed by the Food and Drug Administration, government regulations prohibited the use of bupivacaine. The data from 1973, when bupivacaine became available for clinical use, through 1976 were obtained from a computer-oriented anesthetic record that we routinely employ.[6] Thus, all data were prospective, because as they became available, the person responsible for the evaluation coded them on either the Food and Drug Administration form, the computer-oriented anesthetic record, or computer-designed tally sheets.[6] Data that were not coded from 1973 to 1976 and consequently not retrievable were listed in the tables as "unknown."

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TABLE 1
Number of Blocks Performed and Solution of Bupivacaine Used

Type of block	0.25% Plain	0.25% Epinephrine	0.5% Plain	0.5% Epinephrine	0.75% Plain	0.75% Epinephrine	Total number
Caudal							
Intermittent (continuous) dose	281	639	377	1,368	7	40	2,712
Single injection	36	73	71	246	11	74	511
Epidural							
Intermittent dose	29	57	54	131	9	58	338
Single injection	2	16	75	329	185	2,561	3,168
Peripheral nerve							
Brachial	15	59	10	76			160
Axillary	15	154	5	318			492
Supraclavicular	3	3		11			17
Other	81	557	140	1,275	18	25	2,096
Intercostal	15	308	5	115			443
Intercostal and celiac plexus	30	381	15	220			644
Sciatic plus femoral with or without lateral femoral cutaneous and obturator	42	10	28	31			110
Stellate ganglion	50	88	49	75	10	7	279
Other*	599	2,345	829	4,195	238	2,764	10,970
Total							110
Unknown (dosage and/or block not coded)							
						Grand total	11,080

*"Other" includes the following blocks: (1) maxillary nerve, (2) mandibular nerve, (3) cervical plexus, (4) celiac plexus, (5) sacral plexus, (6) paravertebral lumbar nerves, and (7) other miscellaneous nerves.

The data categories studied were: (1) regional block technic; (2) total milligram doses, ie, volume and concentration; (3) effects of epinephrine content of the solution; (4) area of the surgical or obstetrical procedure; (5) physical status of the patient; (6) Apgar scores; (7) arterial and venous plasma levels; (8) onset of anesthesia; (9) duration of surgery and operative anesthesia; (10) times from injection of the local anesthetic solution until the patient had pain in the operative site; and (11) complications.

RESULTS

Numbers of Blocks:—A total of 11,080 regional blocks were performed with 0.25, 0.5, or 0.75 percent bupivacaine with and without epinephrine (table 1). Of these, 6,599 were for surgical procedures and 3,496 were for obstetrical procedures (table 2). The remaining 985 blocks were for diagnostic and therapeutic procedures.

Dosage (Volume and Concentration) and Epinephrine Content:—For caudal and epidural block, 30 ml or less of solution were injected. Therefore, using 0.25, 0.5, or 0.75 percent solutions, the greatest number of

TABLE 2
Surgical and Obstetrical Procedures Performed Under Bupivacaine Anesthesia*

Area of procedure	Caudal block	Epidural block	Peripheral nerve block
Abdominal wall	8	189	26
Extremity			
Upper			573
Lower	25	67	631
Head and neck			50
Intra-abdominal			
Upper (above umbilicus)	4	258	1,592
Lower (below umbilicus)	14	1,847	66
Obstetrical			
Cesarean	45	344	
Vaginal	2,872	232	3
Thorax			195
Perineum	273	377	16
Other	14	210	145
Total	3,255	3,524	3,297

*Unknown: For 19 blocks, area of procedure or regional block technic was not coded.

TABLE 3
Safe Adequate Dosages (Volumes and Concentrations) of Bupivacaine and Their Indications in Adults for Single-Injection Regional Block Technics*

Type of block	Dosage			Sensory block	Motor block	Indications (operations, manipulations, etc.)
	%	Ml	Mg†			
Epidural	0.75	10-30	75-225	Complete	Complete	Abdominal wall Intra-abdominal Cesarean section Perineum Lower extremity Back surgery (laminectomy, etc.)
	0.5	8-30	40-150	Complete	Moderate to complete	Abdominal wall Perineum Vaginal delivery Lower extremity Diagnostic blocks Therapeutic blocks
	0.25	8-30	20-75	Complete	Minimal to moderate	
Caudal	0.5	8-30	40-150	Complete	Moderate to complete	Perineum Vaginal delivery Lower extremity Diagnostic blocks Therapeutic blocks
	0.25	8-30	20-75	Complete	Minimal to complete	
Peripheral nerve	0.5	5-80	25-400	Complete	Complete	Head and neck Extremities Trunk Perineum Diagnostic blocks Therapeutic blocks
	0.25	5-160	12.5-400	Complete	Moderate to complete	
Local infiltration	0.5	5-80	25-400	Complete	None to complete	Integument system Musculoskeletal system
	0.25	5-160	12.5-400	Complete	None to complete	

*Compiled from previous investigations and confirmed by additional cases.[2-7]

†Solutions with high milligram dose should contain epinephrine.

milligrams administered with these concentrations were 75, 150, or 225, respectively (table 3).

For peripheral nerve block and local infiltration, 160 ml or less of 0.25 percent solution (400 mg) or 80 ml or less of 0.5 percent solution (400 mg) usually were employed (table 3). In this series, for therapeutic purposes *only*, we also performed 60 peripheral nerve blocks with 0.75 percent solution, seeking a longer than usual block, ie, hopefully 48 hours or more, but such times did not occur (table 1). When 80 ml of a 0.5 percent solution was not enough for a peripheral nerve block and a concentration of 0.35 percent or greater was needed to provide rapid establishment of operative anesthesia, the 80 ml was diluted with normal saline to the required volume, usually 100 ml, so that in these instances a concentration of 0.4 percent was used. When this was done, the concentration of the solution was tabulated in table 1 as 0.5 percent.

Of the 11,080 blocks, 9,304 (84 percent) contained epinephrine. We routinely employ epinephrine to slow absorption, prolong duration, and decrease plasma levels of the local anesthetic.[12] Regardless of the volume of the local anesthetic solution, we seldom exceeded 0.25 mg of epinephrine (0.25 ml of a 1:1,000 solution).[13] When 50 ml or less of the local anesthetic solutions were administered, the optimal concentration of epinephrine (1:200,000—ie, 0.1 mg per 20 ml of local anesthetic solution) was maintained.[14] However, if more than 50 ml of

the local anesthetic solution were required, the solution contained less than the optimal concentration, eg, 0.25 mg of epinephrine in 100 ml, or 1:400,000 epinephrine.

Sensory Blockade: — With all regional blocks, concentrations of 0.25, 0.5, or 0.75 percent bupivacaine produced sensory anesthesia of the integumentary and musculoskeletal systems.[2-7] But only 0.75 percent eliminated traction reflexes from the pelvic viscera, reflexes which may be present with weaker concentrations of bupivacaine as well as with other local anesthetic agents (table 3).[6]

Degree of Motor Blockade—The degree of motor blockade varied with the regional block technic and the concentration of bupivacaine (table 3).[2-7] Therefore, motor blockade can be adjusted—"tailored"—to the degree necessitated by the surgical, obstetrical, diagnostic, or therapeutic procedure. Usually, motor blockade occurred 4 to 8 minutes after sensory anesthesia. However, following caudal and epidural blocks, up to 60 minutes may elapse before the maximum degree of motor blockade in the lower extremities results.

Epidural and Caudal Block — When a 0.25 percent solution was employed for single-injection epidural or caudal anesthesia, motor blockade of the muscles of the abdomen, perineum, and lower extremities was minimal. Even with 0.5 percent solutions, motor blockade was incomplete in 20 to 25 percent of the patients. Nonetheless, both of these concentrations were completely adequate for vaginal deliveries, and the 0.5 percent solution was satisfactory for surgical procedures of the abdominal wall, perineum, and lower extremities. But for intra-abdominal surgery, including cesarean sections, as well as for back surgery (laminectomy, disc removal, etc), profound relaxation of the muscles of the abdomen and back occurred consistently only with a 0.75 percent concentration. These statements apply to a single-injection epidural or caudal block technic. With an intermittent (continuous) technic, if the initial injection of a 0.25 or 0.5 percent solution did not produce the desired muscle relaxation, reinforcing (refill) injections usually did.

Peripheral Nerve Block—For peripheral nerve block, 0.5 percent bupivacaine produces profound motor blockade; with 0.25 percent, motor blockade varies from moderate to complete.

Times of Onset and Establishment of Maximum Operative Anesthesia: —These times varied markedly, depending on 3 factors: (1) concentration; (2) volume; and (3) type of block performed.[2-7] Therefore, the results from any single regional block procedure might be atypical. Generally, the higher concentrations and the larger volumes of bupivacaine resulted in the more rapid establishment of operative anesthesia.

Single-Injection Caudal or Epidural Block—With caudal and epidural block, the time of onset of sensory anesthesia with 0.25 and 0.5 percent solutions varied from 4 to 10 minutes, while maximum sensory anesthesia was established in 15 to 35 minutes, depending on the block technic. For example, with epidural block, operative sensory anesthesia of the lower abdomen developed in 15 to 25 minutes, and that of the perineum and lower extremities in 25 to 35 minutes, while with caudal block the opposite sequence occurred. With 0.75 percent solutions, onset of sensory anesthesia was more rapid—3 to 5 minutes—with maximum sensory anesthesia of the lower abdomen following epidural block becoming established in 10 to 20 minutes and that of the perineum and lower extremities in 10 to 30 minutes. Again, with caudal block the reverse sequence resulted.

Peripheral Nerve Block—With peripheral nerve block, the time of onset of sensory block with 0.25 and 0.5 percent solutions varied from 4 to 10 minutes, while maximum sensory anesthesia was established in 15 to 30 minutes.

Duration of Operative Anesthesia:

Single-Injection Technics—In all cases of peripheral nerve or caudal block procedures where 0.25 or 0.5 percent solutions of bupivacaine with or without epinephrine were employed for a surgical procedure, the duration of anesthesia extended beyond the duration of the surgery.[2-4,6] The same was true for epidural or caudal blocks for surgery of the abdominal wall, back, perineum, or lower extremity for which either 0.5 or 0.75 percent solution of bupivacaine with or without epinephrine was used. The operations in some of these cases extended up to 7 hours. Therefore, for these procedures, we have yet to determine the length of time a surgeon can operate following a single dose of bupivacaine as administered by us. The surgery did exceed the duration of operative anesthesia in some cases of intra-abdominal surgery using 0.75 percent bupivacaine

with epinephrine 1:200,000. In these cases, the duration of surgical anesthesia from a single injection of bupivacaine varied from 3½ to 5¼ hours.

Intermittent (Continuous)-Injection Technics—Because of the long duration of bupivacaine, intermittent technics were seldom employed for a surgical procedure. However, intermittent caudal block is our routine technic for vaginal delivery because duration of labor is difficult to anticipate in advance. When intermittent caudal block was contraindicated or when the anesthetist encountered difficulty in placing the needle into the caudal canal, intermittent epidural block was employed.[5]

Using intermittent caudal block and dosages of 15 to 25 ml, the interval between the initial dose of 0.25 percent bupivacaine with epinephrine 1:200,000 and the first reinforcing dose was a mean of 2½ hours with a SD of 1 hour; and 65 percent of the parturients delivered after the initial dose. With 0.5 percent bupivacaine and dosages of 15 to 25 ml with epinephrine 1:200,000, these times were approximately 3⅓ and 1⅓ hours, respectively; and 85 percent of the parturients delivered with only the initial dose.[5,7]

When these concentrations and volumes of 8 to 10 ml were employed for intermittent epidural blocks for vaginal delivery, the duration of anesthesia from the initial and reinforcing doses was shorter than that following caudal block, where larger volumes were administered. With epidural block, perineal anesthesia was occasionally inadequate ("perineal sparing") when 8- to 10-ml volumes were injected. If the parturient who was receiving an intermittent epidural block was ready to deliver and had inadequate anesthesia of the perineum, the anesthetist placed her in a 45° Fowler position and injected 14 to 15 ml of solution. This usually produced perineal anesthesia.

Duration of Postoperative Analgesia: — The interval between injection, the time the anesthesia regressed, and the time complete sensation returned varied widely, depending on the type of block, the concentration and volume of bupivacaine, the area of surgery, and the use of epinephrine.[2-7] Employing stronger concentrations, large volumes, or both produced the longest duration of anesthesia, and the addition of epinephrine usually lengthened these times further. In most regional block procedures, the point at which the majority of the patients required a narcotic for pain was sometime between the regression of anesthesia and complete return of sensation.

Epidural and Caudal Blocks—With these blocks, using single-injection technics, patients required a narcotic for pain in the operative site 6 to 9 hours from the time of injection. The exceptions to this were (1) patients who had rectal or perineal surgery, including episiotomies, who did not request a narcotic until 60 to 185 minutes after complete sensation had returned; and (2) patients who had either orthopedic surgery involving the hip and the lower extremity or genitourinary surgery involving the perineum (prostate, bladder, etc); these patients often never needed a narcotic for pain relief.

Peripheral Nerve Block—The time when the patient required a narcotic for pain in the operative site with peripheral nerve block varied significantly with the block technic, as follows: (1) maxillary or mandibular nerves or their branches, 10 to 12 hours; (2) brachial plexus blocks, 8 to 20 hours; (3) intercostal nerve blocks, 8 to 18 hours; and (4) sciatic and femoral nerve blocks with or without lateral femoral cutaneous nerve and/or obturator nerve block, 14 to 30 hours. With the exception of intercostal nerve blocks, which we commonly employ for upper intra-abdominal surgery, many of the patients who had orthopedic procedures (closed reductions, bunionectomies, etc) required no narcotics postoperatively.

Plasma Levels: — Peak arterial whole-blood levels were 20 to 40 percent higher than simultaneously sampled venous whole-blood levels, and they occurred earlier (fig 1 and 2; table 4).[2,5,8,9] The arteriovenous differences persisted for about 1 hour after injection. When whole blood was separated into plasma and erythrocytes, the greater amount of bupivacaine (more than 90 percent) was found in the plasma.[15]

Single-Injection Technics—In adult patients, single-injection caudal or epidural blocks may require 225 mg of bupivacaine with epinephrine, and some peripheral nerve blocks, 400 mg with epinephrine. When a dose of 400 mg or less was employed, arterial and venous plasma levels following single-dose blocks did not exceed 4 μg/ml, a level *above* which systemic toxic reactions are *"believed"* to occur (fig 1 and 2; table 4).[8,9,16]

Intermittent (Continuous)-Injection Technics—As with all other amide derivatives, levels of bupivacaine in such technics in-

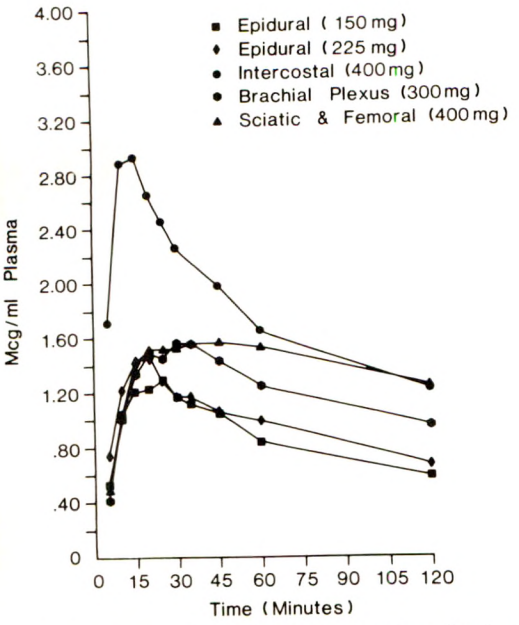


FIG 1. Means of arterial plasma levels of bupivacaine in 10 patients for each of the 5 blocks prior to the block, and then at intervals of 5, 10, 15, 20, 25, 30, 45, 60, and 120 minutes (from Moore et al[10]).

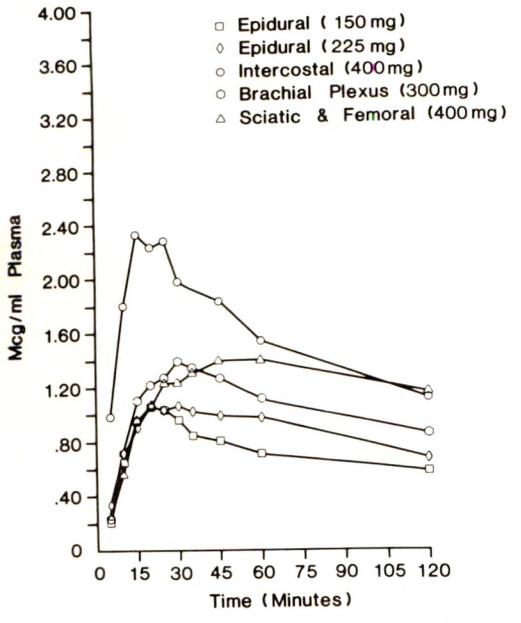


FIG 2. Means of venous plasma levels of bupivacaine in 10 patients for each of the 5 blocks prior to the block, and then at intervals of 5, 10, 15, 20, 25, 30, 45, 60, and 120 minutes (from Moore et al[10]).

crease with each reinforcing injection, ie, cumulation occurs. However, seldom is more than 1 reinforcing injection of 0.5 percent bupivacaine required.[2,5] In our cases, when cumulative arterial and venous plasma levels were measured, they had not reached 2 μg/ml.[5]

Placental Transfer and Infant Depression: —Placental transfer of bupivacaine occurs, but when arterial and venous plasma levels of the newborn were compared to those of the mother, the amount of placental transfer was minimal.[5] The Apgar scores of our newborns—at 5 minutes, 94 percent scored 8, 9, or 10—indicated that bupivacaine did not cause depression of the newborn (table 5). Neurobehavioral testing of infants by others supports this finding.[17]

Complications: —With the exception of the following, there were no untoward reactions to bupivacaine, that is, no neurologic complication, no tissue damage, or the like.

Total Spinal—Following caudal block 1 patient experienced a total spinal anesthesia following injection of 22 ml of 0.5 percent with epinephrine, but her pulse rate and blood pressure were not altered. She was given artificial respiration through an endotracheal tube. Adequate respirations returned in approximately 2 hours and 45 minutes. Complete sensation returned 11 hours and 55 minutes after the injection. To date, the patient has had no untoward sequelae.

Generalized Systemic Toxic Reactions (Table 6)—In the 11,080 blocks, systemic toxicity occurred from unrecognized intravascular injections in 13 patients (0.12 percent) and from absorption in 2 patients (0.018 percent). Twelve of these 15 patients convulsed, and 3 had milder signs and symptoms. All reactions were recognized immediately and treated rapidly and correctly, and no untoward sequelae resulted.[13] In 2 other patients, inadvertent intravascular injections produced no signs or symptoms of systemic toxicity.

The intravascular injections resulted during attempts to administer caudal or epidural block. When, as in these cases, all tests to avoid such an intravascular injection were performed and they indicated that the needle or plastic tubing did not lie within the lumen of a blood vessel, such reactions can be considered unavoidable.

The other 2 reactions in young, healthy patients resulted from absorption following intercostal nerve block. Why they occurred is open to question. Perhaps the dosages of bupivacaine were responsible. However, the same or larger doses of bupivacaine have

TABLE 4
Mean and Range of Peak Microgram Levels of Bupivacaine Per Milliliter of Arterial and Venous Plasma*

Block	Dosage %	Dosage Ml	Dosage Mg	Arterial Mean	Arterial Range†	Venous Mean	Venous Range†
Epidural‡	0.5	30	150	1.46	1.10-2.32	1.19	0.71-1.73
	0.75	30	225	1.49	1.12-2.15	1.25	0.78-1.70
Brachial plexus (supraclavicular approach)§	0.5	60	300	1.71	1.05-2.40	1.55	0.94-2.25
Sciatic plus femoral nerve with or without lateral femoral cutaneous or obturator nerve blocks‖	0.5	80	400	1.89	1.00-3.16	1.60	0.84-2.73
Intercostal nerve (bilateral)‖	0.5	80	400	3.29	1.72-4.00	2.52	1.40-3.45

*Compiled from Moore et al[8,9]
†Range = low to high
‡Solution contained epinephrine 1:200,000
§Solution contained epinephrine 1:240,000
‖Solution contained epinephrine 1:340,000

TABLE 5
Apgar Scores Following Bupivacaine

Apgar scores	0.25% 1 min	0.25% 5 min	0.5% 1 min	0.5% 5 min	0.75%* 1 min	0.75%* 5 min
0	19	19	21	22	8	8
1 or 2	22	1	50	0	15	9
3 or 4	31	3	63	12	17	1
5, 6, or 7	201	46	439	82	85	17
8, 9, or 10	812	1,014	1,474	1,931	184	274
Total	1,085	1,083	2,047	2,047	309	309

*0.75 percent solutions were used for cesarean sections only.

been used for intercostal nerve blocks, as well as for various other peripheral nerve blocks, with no such reactions (table 7). In 1 case, the solution did not contain epinephrine. This may have been a factor. Or perhaps in both patients, it was the site of the injection. Of all regional block technics investigated to date, intercostal nerve block produces the highest plasma levels, regardless of the local anesthetic drug administered (fig 1 and 2; table 4).[8,9,12,19,20] On the other hand, maybe none of these—technic, absence of epinephrine, or dosage of bupivacaine—was the initiating factor. In these 2 cases, it may have been the patient's individual toxic threshold. This is difficult to determine prior to a specific regional block because blood levels vary according to the site of injection. In many patients, and in particular those with a poor physical status, we routinely use 300 mg or more of 0.35 to 0.5 percent bupivacaine with epinephrine (tables 7 and 8). Of the 2,093 intercostal nerve blocks administered from 1973 through 1976, 624 were done with 300 mg or more, and no such reactions resulted in 241 patients (39 percent) with a poor physical status, ie, American Society of Anesthesiologists physical status ratings of 3, 4, or 5.[18]

Shivering—Shivering has been cited as possible evidence of a mild systemic toxic reaction after administration of bupivacaine, and it was observed in this study.[4] Shivering did not occur when operating room temperatures were 74° F (23.3° C) or above, but did when temperatures were 70° F (21.1° C) or below.[8,9] Shivering may result from a number of variables, such as room temperature or degree of block of the sympathetic nervous system; the least important is the local anesthetic.

TABLE 6

Toxic Responses of Patients Having Intravascular Injections or Rapid Absorption of Bupivacaine

Surgery	Total, mg	Conc, %	Epinephrine content	Age, yrs	Weight Lbs	Weight Kg	Height Inches	Height Cm	Physical status (ASA scoring)	Type of reaction	Degree of anesthesia	Definitive type of anesthesia and dosage used for surgical or obstetrical procedure
Intravascular injection												
Epidural block												
Vaginal hysterectomy	135	0.75	1:200,000	43	133	60.5	66	165	2	Convulsion	None	Spinal block, tetracaine (8 mg)-dextrose (80 mg)
Abdominal hysterectomy	75	0.75	1:200,000	59	165	75.0	68	170	1	Convulsion	None	Spinal block, tetracaine (10 mg)-dextrose (100 mg)
Ureterectomy*	112	0.75	1:200,000	65	123	55.9	63	158	2	Convulsion	None	General anesthesia
Vaginal hysterectomy	150	0.75	1:200,000	65	121	55.0	64	160	1	Convulsion	None	General anesthesia
Caudal block												
Removal of hip pin	188	0.75	1:200,000	79	144	65.5	57	143	2	Convulsion	None	Local infiltration, lidocaine 1%, 40 ml
Tumor of hip	172	0.75	1:200,000	66	186	76.4	69	173	3	Convulsion	None	Epidural block, bupivacaine 0.75%, 13 ml‡
Absorption												
Bilateral intercostal nerve block												
Therapeutic block	300	0.5	None	28	130	59.1	65	163	1	Convulsion	Satisfactory block	
Cholecystectomy	425	0.40	1:500,000	22	101	45.9	60	150	2	Convulsion	Satisfactory block	
Obstetrics												
Intravascular injection												
Caudal block*												
Vaginal delivery	40	0.25	None	24	125	56.8	65	163	1	None	None	Plastic tubing withdrawn, reinserted in caudal canal, bupivacaine 0.25%, 16 ml

TABLE 6 (continued)
Toxic Responses of Patients Having Intravascular Injections or Rapid Absorption of Bupivacaine

Surgery	Total, mg	Conc, %	Epinephrine content	Age, yrs	Weight Lbs	Weight Kg	Height Inches	Height Cm	Physical status (ASA scoring)	Type of reaction	Degree of anesthesia	Definitive type of anesthesia and dosage used for surgical or obstetrical procedure
Vaginal delivery	100	0.5	1:200,000	21	130	59.1	64	160	1	Mild cerebral†	None	Plastic tubing withdrawn, reinserted in caudal canal, bupivacaine 0.5%, 20 ml‡
Vaginal delivery	120	0.5	1:200,000	20	127	57.7	67	168	1	Mild cerebral†	None	Plastic tubing withdrawn, reinserted in caudal canal, bupivacaine 0.5%, 20 ml‡
Vaginal delivery	50	0.25	1:200,000	27	155	70.5	63	158	1	Tinnitus	None	Plastic tubing withdrawn, reinserted in caudal canal, bupivacaine 0.25%, 20 ml‡
Vaginal delivery	42	0.25	1:200,000	24	158	71.8	65	163	1	None	None	Plastic tubing withdrawn, reinserted in caudal canal, bupivacaine 0.25%, 17 ml‡
Vaginal delivery	100	0.5	1:200,000	23	142	64.6	63	158	1	Convulsion	None	Plastic tubing withdrawn, reinserted in caudal canal, bupivacaine 0.5%, 20 ml‡
Vaginal delivery	120	0.5	None	24	150	68.2	66	165	1	Convulsion	None	Plastic tubing withdrawn, reinserted in caudal canal, bupivacaine 0.5%, 20 ml
Vaginal delivery	100	0.5	1:200,000	22	131	59.6	67	168	1	Convulsion	None	Spinal block, tetracaine (6 mg)-dextrose (60 mg), patient ready to deliver
Vaginal delivery	120	0.5	1:200,000	28	170	77.3	62	155	1	Convulsion	None	Pudendal block, lidocaine 1% (3 ml), patient ready to deliver

*Plastic tubing was placed initially in these patients.

†Mild cerebral = anxiety, nervousness, and inability to answer questions rationally.

‡Solution contained epinephrine 1:200,000.

TABLE 7

Number of Patients and Milligrams of Bupivacaine Administered for Commonly Used Single-Injection Blocks, 1966 to 1976

Single-injection blocks	Dosage range, mg	Total number of patients
Epidural	150 or less	2,892
	151-200	160
	201-250	73
	251-300	8
		3,133*
Brachial plexus	150 or less	247
	151-200	91
	201-250	167
	251-300	123
	301-350	12
	351-400	17
	401-450	7
	451-525	2
		666*
Sciatic with or without femoral, lateral femoral cutaneous, and obturator	150 or less	74
	151-200	78
	201-250	240
	251-300	114
	301-350	67
	351-400	42
	401-450	25
	451-600	3
		643*
Intercostal (bilateral and unilateral) with or without celiac plexus block	150 or less	567
	151-200	261
	201-250	659
	251-300	645
	301-350	163
	351-400	136
	401-450	88
	451-600	11
		2,530*

*Unknown: Dosages were not coded for 35 epidural, 3 brachial plexus, 1 sciatic, and 9 intercostal nerve blocks. Therefore, these block technics could not be tabulated, which explains the discrepancy between the total number of blocks in this table as compared to table 1.

TABLE 8

Dosages of Bupivacaine Compared to Physical Status, March 1973 through June 1976*

Dose, mg	Physical status (number of patients)† 1	2	3	4	5	Total
150 or less	4,238	1,253	288	34	3	5,816
151-200	439	171	60	4	0	674
201-250	456	321	147	22	0	946
251-300	315	388	198	27	0	928
301-350	57	66	18	3	1	145
351-400	110	89	27	4	0	230
401-450	71	46	19	7	1	144
451-500	2	3	3	0	0	8
501-550	1	2	1	0	0	4
551-600	1	2	1	0	0	4
601 or more	4	1	0	0	0	5
Total	5,694	2,342	762	101	5	8,904
Unknown (dose or status not coded)						99
						9,003

*Bupivacaine became available for clinical use in March 1973. During the investigative period (1966 to 1968), the largest dose of bupivacaine which could be employed was restricted to 250 mg with epinephrine.[2] Thus, to avoid a false impression of the distribution of the dosage now in use, the 2,077 blocks done during the investigative period were not included in this table.

†American Society of Anesthesiologists Physical Status Ratings.[18]

CONCLUSIONS

Quality of Anesthesia:—Bupivacaine is a reliable, versatile, long-acting local anesthetic. When used in the correct dosage (volume and concentration) for caudal, epidural, and peripheral nerve blocks, it produces complete sensory blockade while allowing the degree of motor blockade to be adjusted to the requirements of the surgical, obstetrical, diagnostic, or therapeutic procedure.

When administered for caudal, epidural, or peripheral nerve block, or for local infiltration, the duration of anesthesia from bupivacaine is 2 to 3 times longer than lidocaine (Xylocaine®) or mepivacaine (Carbocaine®) and 20 to 25 percent longer than tetracaine (Pontocaine®).[2-4] When compared to etidocaine (Duranest®) for epidural and caudal block, bupivacaine has a significantly longer duration of sensory blockade and a significantly higher incidence of satisfactory sensory blockade.[6,7] As for the other variables—times of onset and establishment of operating anesthesia, degree of relaxation of the abdominal musculature, etc—bupivacaine is comparable with these other local anesthetic drugs, provided the correct dosages (concentrations and volumes) of bupivacaine as required by the surgical, obstetrical, diagnostic, or therapeutic procedures are employed. For example, for intra-abdominal surgery employing epidural block or for peripheral nerve block 0.75 percent and 0.5 percent, respectively should be used for rapid establishment o

operating anesthesia, as well as complete motor blockade—not weaker concentrations.

Indications:—The long duration of action of bupivacaine makes it the local anesthetic drug of choice for the hospitalized patient, particularly in a teaching institution, when the anesthesiologist selects caudal, epidural, or peripheral nerve block or local infiltration for a long surgical or obstetrical procedure, for relief of postoperative or chronic pain, or to produce prolonged vasodilation of an extremity.

Safety: — Bupivacaine is an extremely safe local anesthetic drug. The number of complications which occurred were minimal, and no sequelae resulted from them. The complications were those that could be expected following the administration of a caudal, epidural, or peripheral nerve block, regardless of the local anesthetic drug injected.

While complications seldom occur with bupivacaine or with other local anesthetic drugs, it behooves the physician employing regional blocks to be able to recognize a complication from them immediately and treat it properly. Unfortunately, all too often when a complication occurs, attention is focused on the dosage of the local anesthetic drug, rather than on the ability of the physician employing the drug.

Dosage: —As yet the maximum dose of bupivacaine in humans has not been determined. In the United States, where 0.25, 0.5, and 0.75 percent solutions are available, no maximum dosage is defined in the package insert, which states: (1) "Most experience to date is with single doses of Marcaine up to 225 mg with epinephrine 1:200,000, and 175 mg without epinephrine; more or less drug may be used depending on individualization of each case"; and (2) "In clinical studies to date, total daily doses have been up to 400 mg. Until further experience is gained, this dose should not be exceeded in 24 hours."* However, some physicians have misinterpreted the 1st of these statements to mean that the doses stated represent the maximum amounts that should be given.

In countries other than the United States, where only 0.25 and 0.5 percent bupivacaine is available, the maximum dosage of bupivacaine is stated as 2 mg/kg, with a maximum dosage of 100 mg without epinephrine and 150 mg with epinephrine 1:200,000.† These restrictive doses are open to question. First, they apparently were determined primarily not by clinical studies in humans, but by extrapolation of animal data to humans based on equitoxic and equipotent doses of bupivacaine, lidocaine, mepivacaine, and tetracaine and using the extrapolated data to establish *1* maximum dose, calculated on the patient's weight, for *all* regional block technics.[21] Second, to establish a single maximum dose in humans of bupivacaine or any other local anesthetic drug on such a basis is unfortunate. Doing so overlooks the fact that blood levels of a local anesthetic in humans vary, depending on the site of its injection.[8-10,19,20] Third, use of extrapolated data ignores the facts that detoxification mechanisms in humans and animals differ, that distribution and detoxification in humans may not be the same for all local anesthetic drugs, and that for the same local anesthetic drug these mechanisms vary from human to human, as shown by plasma levels.[8,9] Finally, in our 11,080 regional blocks, only 2 reactions (0.018 percent) have occurred from absorption following doses of bupivacaine significantly larger than those recommended outside the USA (tables 6 to 8). These 2 complications were the only complications that might have been prevented by using a smaller dose. Therefore, to eliminate the use of bupivacaine in many patients—particularly those with a poor physical status where regional block technics performed with a long-acting drug are the anesthetic method of choice—by unwarranted restrictive dosages based principally on animal data is not in the best interests of patient care.

These investigations, involving 11,080 regional blocks, show that in the adult patient, *regardless of physical status,* the following doses are safe: For single-dose caudal or epidural block, 0.25, 0.5, or 0.75 percent solutions of bupivacaine with epinephrine 1:200,000 can be administered in amounts of 225 mg or less. For single-dose peripheral nerve block or local infiltration, 0.25 or 0.5 percent solutions of bupivacaine can be injected in amounts of 400 mg or less, with volumes and epinephrine content being var-

*Package insert of Winthrop Laboratories (revised October 1974), New York, New York

†As stated in package inserts from Australia, Brazil, England, France, Germany, Japan, Netherlands, and New Zealand; British Pharmaceutical Codex, Pharmaceutical Press of London, 1973, and Martindale: The Extra Pharmacopoeia, 26th edition, Pharmaceutical Press of London, 1967. Copies supplied on request.

ied to meet the requirement of the block technic. This does not imply that these doses should be used in all instances. As regional block technics are mastered, volumes and thus total milligram doses smaller than those we routinely administer may produce satisfactory results. If they do, then such smaller doses should be used.

Readers are cautioned that the 0.75 percent solution of bupivacaine available in the USA was developed for use only in single-injection epidural or caudal block or for the initial dose when an intermittent-injection technic for these blocks is employed in a surgical procedure. It is not used by us for peripheral nerve block technics except for an occasional therapeutic indication. If this concentration is employed for peripheral nerve block in the volumes described herein, systemic toxic reactions might occur more frequently from absorption, because the higher the concentration of a local anesthetic using the same milligram dose, the higher the blood level of the agent.[12] Furthermore, neither the duration of action of the 0.75 percent solution nor its effect on peripheral nerves has been thoroughly investigated.

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Control of Hypertension During Cardiopulmonary Bypass with Cryptenamine

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Cryptenamine, a mixture of veratrum alkaloids which induces "physiological" hypotension by acting upon sensory hypotensive receptors, was used in 18 patients during cardiopulmonary bypass under morphine anesthesia when mean arterial pressures exceeded 100 torr. In 10 patients, the drug was infused into the oxygenator reservoir (group 1); in the other 8 patients, it was infused directly into the arterial inflow line (group 2.) Infusion was titrated to achieve average mean perfusion pressures between 70 and 80 torr. Immediately prior to drug infusion, control values (mean ± SE) for group 1 were blood pressure 107 ± 3.3 torr, pump flow 64.9 ± 2.9 ml/kg/min, and calculated systemic vascular resistance 2017 ± 74 dyne-sec-cm^{-5}; and for group 2 blood pressure 110 ± 3.0 torr, pump flow 63.4 ± 1.7 ml/kg/min, and resistance 2002 ± 113 dyne-sec-cm^{-5}. There was no statistically significant difference in these control values between the two groups. After the start of infusion, mean values were the following for group 1: total dose of cryptenamine 28.7 ± 3.3 μg/kg; average infusion rate 2.4 ± 0.3 μg/kg/min; latency of onset 5.9 ± 1.2 minutes; lowest pressure reached 57 ± 3.2 torr; onset of recovery 28.0 ± 5.9 minutes after the end of infusion; time to 50 percent recovery 39.2 ± 5.9 minutes; lowest resistance 987 ± 56 dyne-sec-cm^{-5}; and average pump flow during infusion 68 ± 3 ml/kg/min. Group 2 differed significantly ($p<0.05$) in all but the last 2 variables, the other values being: total dose 15.5 ± 3.7 μg/kg; infusion rate 1.4 ± 0.2 μg/kg/min; latency 0.9 ± 0.2 min; start of recovery 10.0 ± 3.2 min; 50 percent recovery 22.3 ± 6.2 min; and lowest pressure reached 70 ± 3.6 torr. Differences in magnitude and duration of drug action between the 2 groups are probably due to necessarily different drug concentrations in blood supplying the aortic and carotid receptor areas. In all patients, urine output during bypass (606 ± 83 ml during 89.7 ± 5.5 minutes perfusion time) and arterial and mixed venous blood gases were unaffected. All patients came off bypass quickly (separation time 1.9 ± 0.4 minutes) and easily, and all but 1 recovered uneventfully. Possible advantages of cryptenamine, given by titrated infusion into the arterial line, over alternative methods of controlling hypertension during bypass include (1) smooth control of blood pressure without a deleterious reflex increase in cardiac sympathetic tone, which may accompany hypotension brought about by directly acting peripheral vasodilators; (2) lack of lingering central nervous system or cardiac depression; (3) the presence of a physiological pressure bottom (when vasomotor tone reaches 0); and (4) absence of toxic metabolites.

Key Words—ANESTHETIC TECHNICS, hypotensive. ANESTHESIA, cardiovascular. SURGERY, cardiovascular. BLOOD PRESSURE, cryptenamine. SYMPATHETIC NERVOUS SYSTEM, sympatholytic agents, cryptenamine.

DEVELOPMENT of high arterial blood pressure during anesthesia and surgery is a relatively new concern. The increased use of light, "balanced" anesthesia in recent years is, of course, associated with reduced blood and tissue levels of general anesthetics, and thus a reduction of their accompanying depression of cardiovascular function both centrally and by direct peripheral actions. Hence the probability that hypertension will occur has increased. At the same time our awareness of the possible undesir-

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able consequences of high blood pressure is greater.[1]

During the early days of the use of morphine as the main anesthetic during open heart operations, a major concern was not hyper- but hypotension.[2] However, more recently, reports of high blood pressures during these procedures have become more frequent.[3-5] This has been viewed with concern. Indeed, ECG changes of myocardial ischemia associated with hypertension[6] have been observed, thus pointing out the particular vulnerability of patients with diseased coronary arteries to hypertensive episodes during anesthesia. An abnormal increase in blood pressure during open heart operations today is generally regarded as an indication for more or less vigorous efforts to reduce it. The 2 primary measures taken for this purpose have been (1) increased administration of central nervous system and cardiac depressants, such as general anesthetics, neuroleptics, or benzodiazepine-type drugs, or (2) injection or infusion of peripheral vasodilators such as sodium nitroprusside or nitroglycerin. Both measures may have undesirable consequences. The 1st violates the principles which led to "lighter" anesthesia in the 1st place and especially to the use of potent analgesics. No conclusive evidence has been presented that the chemical insult to the myocardium is harmless, especially in patients whose heart is the target organ for surgical intervention. Nitroprusside and nitroglycerin, on the other hand, act peripherally to reduce blood pressure without concomitant myocardial or central nervous system depression, and hence must be expected to lead reflexly to increased cardiac sympathetic tone[7,8]—with consequent increase in cardiac metabolic requirements, often in the face of lowered coronary perfusion pressure.

Casting about for a means to lessen the cardiac load and at the same time minimize cardiac sympathetic neurogenic tone (and hence metabolism), we turned to the drug cryptenamine (Unitensin®), a mixture of antihypertensive veratrum alkaloids prepared from *Veratrum viride* standardized by bioassay. The active alkaloids in cryptenamine are polyesters of the alkamines germine and protoverine. These naturally occuring esters differ only in their absolute potency and in their time course, and animal observation has shown that the mechanism of action of all of these esters is basically the same.[9] They act by stimulating or sensitizing afferent sensory endings, among them those in the left ventricle, the lungs, and the baroreceptors, especially those located in the aortic arch and the carotid sinus. Therefore, these drugs reflexly lower both sympathetic vasomotor tone and cardiac neurogenic tone[9] (fig 1). The main deterrent to their wider clinical use has been the narrow ratio between the dose causing hypotension and that producing nausea and vomiting. This represents no problem in anesthetized patients, especially in those who have received large doses of morphine, known to depress the emetic center.[10] For these reasons, we undertook the present study, the initial phase of which is presented here. In this part of the study, we attempted to answer the question of whether or not drugs of this type could be used to alleviate the rise in peripheral resistance seen during extracorporeal perfusion with resultant undesirably high perfusion pressures and, all too often, reduction of pump flow to inadequate levels in an effort to compensate for this rise. The question is important because (1) some of the sites of action of these compounds are not perfused during bypass, and (2) it is possible that the in

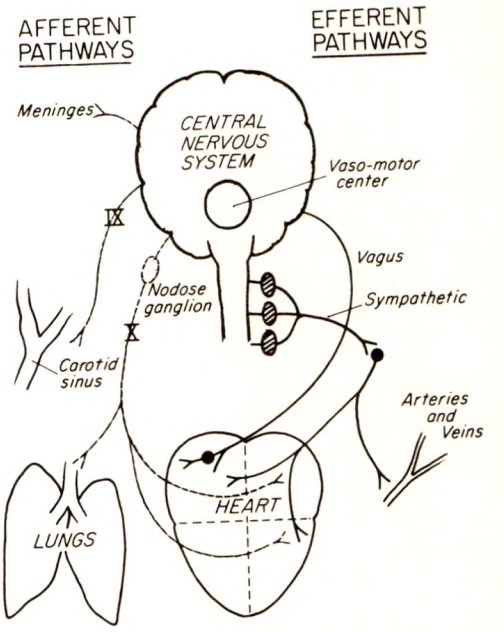


FIG 1. Afferent and efferent pathways involved in the action of cryptenamine. Afferents are shown on the left, efferents on the right side. The efferent response to stimulation or sensitization of afferent receptors in the carotid sinus, heart, and/or lungs consists of a decrease in sympathetic outflow to the heart and to the vasculature, and an increase in vagal tone.

crease in resistance observed during perfusion is caused and maintained by humoral rather than neurogenic mechanisms.[11-13] The results answer this question affirmatively; that is, cryptenamine is effective in lowering blood pressure during cardiac bypass. Future studies may extend its use to the pre- and post-bypass periods, when hypertension can be as troublesome a problem as during cardiopulmonary bypass.

METHODS

Thirteen male and 4 female patients with coronary artery disease and 1 male patient with aortic valve disease received cryptenamine. These 18 patients, who ranged in age from 41 to 72 years (mean age 57) and fell into ASA Physical Status Categories 3 and 4, were part of a larger group of patients treated in various ways for control of hypertension during cardiac bypass. All patients gave informed consent for control of possible hypertension by appropriate means, including cryptenamine, and for the use of any data obtained.

The patients were premedicated with morphine, scopolamine, and diazepam. Appropriate monitoring lines were placed for continuous measurement oscillographic and digital display and recording (Hewlett Packard, Series 7700 System) of direct radial arterial and central venous pressures, ECG, and tympanic or nasopharyngeal temperature. Urine output was measured continuously; blood samples for arterial and mixed venous blood gases, serum electrolytes, and hematocrits were obtained at intervals as deemed necessary.

After 5 minutes of breathing 100 percent O_2 (6 L/min by mask), patients were anesthetized with 2 mg/kg morphine sulfate IV in 150 ml 5 percent dextrose in water at a rate of 5 to 10 mg morphine/min. This was supplemented by 5 to 15 mg diazepam in divided doses. Depending upon initial blood pressure, some patients also received up to 1.5 percent enflurane in O_2. Ventilation was gradually taken over by the anesthetist, and after consciousness was lost, pancuronium 0.1 mg/kg was given intravenously, 2 ml of 4 percent lidocaine was instilled into the trachea, and endotracheal intubation was carried out. After intubation, 50 percent N_2O was started while enflurane was continued (up to 2.5 percent) as needed, ventilation being controlled with a constant-volume ventilator to maintain arterial Po_2 at 100 torr or greater and Pco_2 between 35 and 40 torr.

The chest was opened via median sternotomy, aortic arch and right atrial cannulations were carried out, and extracorporeal perfusion was begun. When the ascending aorta was cross clamped during perfusion, the aortic root (coronary arteries in the patient who had the aortic valve replacement) was perfused via a separate cannula and pump with ice-cold blood, resulting in ventricular fibrillation and heart muscle temperatures in the range of 14 to 20° C.[14] Mean time from completion of the morphine infusion until institution of cardiac bypass was 55 minutes (range 42 to 70 minutes); hence, no additional morphine was added to the pump. Enflurane, if used, was discontinued prior to aortic cannulation and not administered again.

Throughout perfusion, pump flows were maintained at about 70 ml/kg/min (or 2.4 L/m^2 min). When and if the mean perfusion pressure (radial artery) rose above 100 torr, infusion of cryptenamine* was started. The average time (for all patients) between the beginning of cardiac bypass until the start of cryptenamine was 37 minutes (range 15 to 75 minutes). The drug was mixed in 5 percent dextrose in water in a concentration of 100 μg/ml and infused by means of a Harvard Apparatus Company continuously variable constant infusion pump. In the first 10 patients (group 1), the cryptenamine was given into the reservoir of the Galen bubble oxygenator, in which cases the extracorporeal volume (between infusion site and patient) varied from about 600 to 1700 ml, depending upon the volume present in the oxygenator at that time. As this was found to be less than satisfactory for blood pressure control (see Results and Discussion), the succeeding 8 patients (group 2) received the cryptenamine by constant infusion directly into the arterial inflow line to the aortic arch cannula (just before the filter). In these patients, the total volume between infusion line and patient remained constant at less than 200 ml. Drug infusion rates were titrated according to the patient's response to keep pressures at about 75 to 80 torr.

Changes in mean blood pressure and systemic vascular resistance produced by cryptenamine (ie, differences between control values just prior to drug infusion and values

*Unitensin,® generously supplied by Malinkrodt Laboratories in ampules containing 2 ml of drug in a concentration of 260 carotid sinus reflex (CSR) units = 2 mg/ml, as presently marketed for IV use.

TABLE

Effects of Cryptenamine Infusions

Patient	Pump time before infusion (min)	Mean blood pressure (torr) Minutes after start of drug infusion 0 (control)	3	5	8	10	15	20	25	30	35	40	Lowest blood pressure (torr)	Total dose (μg/kg)	Infusion rate (μg/kg/min)	Duration of infusion (min)
Group 1																
1	44	115	115	120	132	140	110	70	55	60	68	85	55	14.7	0.70	21
2	52	130	134	132	110	102	74	75	—	—	100	113	60	18.3	1.67	12
3	19	115	115	135	135	126	130	96	62	60	62	72	60	44.7	2.24	20
4	16	100	105	99	92	85	71	76	73	62	70	73	75	29.6	2.22	14
5	15	108	110	110	103	96	60	50	45	50	50	50	45	47.7	4.33	13
6	21	100	110	100	90	70	60	63	70	70	71	75	60	20.8	2.31	9
7	43	95	95	110	75	61	50	50	51	51	51	53	40	36.8	3.97	8
8	75	100	100	100	100	86	72	68	65	73	82	88	65	34.3	2.85	12
9	35	106	100	95	86	80	58	50	51	54	58	61	50	25.4	1.75	12
10	49	105	106	109	84	72	65	65	75	81	82	80	60	14.9	1.87	7.5
Mean	37	107	109	111	101	92	75	66	61	62	69	75	57	28.7	2.4	12.9
SE	±6.2	±3.3	±3.5	±4.4	±6.3	±7.9	±8.4	±4.6	±3.6	±3.5	±4.9	±5.8	±3.2	±3.3	±0.3	±1.5
Group 2																
11	49	125	101	99	77	75	77	92	100	100	100	100	70	8.9	1.37	6.5
12	27	110	110	108	90	76	80	80	80	80	93	100	70	15.3	1.61	9.5
13	30	120	110	97	80	76	98	103	105	104	104	113	65	8.3	1.84	4.5
14	41	105	80	72	83	87	99	101	101	105	112	112	70	3.9	0.78	5.0
15	26	105	94	94	95	96	90	90	93	101	105	105	85	37.5	2.14	20.5
16	60	105	100	103	96	94	83	61	57	52	54	58	50	15.3	0.77	4.5
17	35	108	107	105	93	88	80	77	83	70	73	77	77	21.7	1.74	12.0
18	16	100	109	110	104	82	67	65	65	65	65	66	65	13.2	0.97	13.5
Mean	36	110	101	99	90	84	84	84	86	85	88	91	70	15.5	1.4	11.1
SE	±5.2	±3.0	±3.7	±4.2	±3.2	±2.9	±3.8	±5.5	±6.2	±7.3	±7.6	±7.5	±3.6	±3.7	±0.2	±2.1
p (group 1 vs group 2)	NS	NS	NS	NS	NS	NS	NS	<0.05	<0.01	<0.02	<0.05	NS	<0.05	<0.05	<0.05	NS

during infusion) and in average pump flow, total drug dose, rate of infusion, latency, and time to recovery were tabulated and the means ± SE for each variable were calculated for each group. Comparison between groups 1 and 2 was done by means of Student's *t*-test for unpaired data. Differences between the two groups were considered significant at a p value of <0.05.

RESULTS

The infusion of cryptenamine decreased the blood pressure of all patients, whether the drug was given into the oxygenator reservoir (group 1) or infused into the arterial line (group 2).

Groups 1 and 2 were similar in age, weight, blood pressure, pump flow, and calculated resistance prior to bypass (controls); statistically the differences between the 2 groups were $p>>0.1$. Nevertheless, there were marked differences between the groups in latency of onset of the fall in blood pressure, as well as in duration and magnitude of response (see table and fig 2 to 5). The table shows values for individual patients at the start of infusion and at various intervals thereafter. For clarity, the means ± SE of these values are also presented graphically in fig 2. In group 1 the latency period (from the start of infusion until blood pressure began to decrease) varied greatly among patients, and in 7 of the 10 there was a continuing rise in pressure before the onset of the fall. When we increased the rate of infusion to shorten the latency, the maximal pressure fall was frequently greater than desired. The patients in group 2 behaved quite differently; the latency was much shorter and more uniform (fig 2, fig 4, table), and a further rise in pressure was seen in only 1 patient. There was better control of the magnitude of pressure fall and recovery was more rapid (fig 3). Because of the small number of patients in both groups, the different durations of the infusions (see table), and the wide scatter of the group 1 values, differences in mean arterial pressure between the 2 groups were statistically significant ($p<0.05$) only at 20 minutes or more after the start of infusion (fig 2). Although there was no difference in mean values of blood pressure between the 2 groups at the time the infusion was stopped (time 0 in fig 3), the pressures in the group 1 patients (broken line) tended to "overshoot"; that is, they dropped still lower for 10 to 15 minutes before the start of recovery (see table). This was not true for patients in group 2; hence, mean values for pressures were significantly different between the 2 groups at all times during recovery, with pressures in group 2 running from 10 to 20 torr higher (fig 3).

Figures 4 and 5 illustrate graphically more details of the differences in drug action according to the site of infusion, namely,

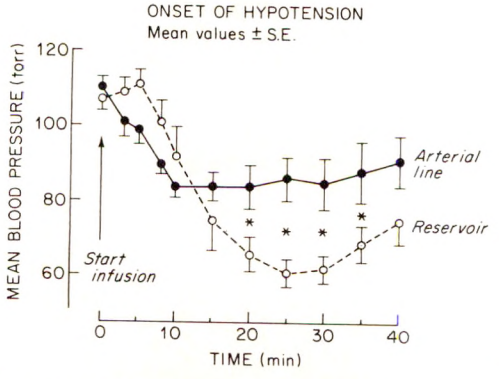


FIG 2. Mean values (± SE) for blood pressure response to cryptenamine in the 2 groups of patients, those in whom the drug was infused into the reservoir and those in whom the drug was infused into the arterial line from the extracorporeal pump. Time after the start of the infusion is shown on the abscissa; integrated mean radial artery pressure is on the ordinate. The broken line represents the statistical mean values of pressure for the 10 patients in whom the drug was infused into the reservoir (group 1); the solid line represents the mean values for the 8 patients who received the drug into the arterial line (group 2). Asterisks designate a significant difference between the two groups ($p<0.05$). The delay in onset and the greater drop in pressure in group 1 is evident.

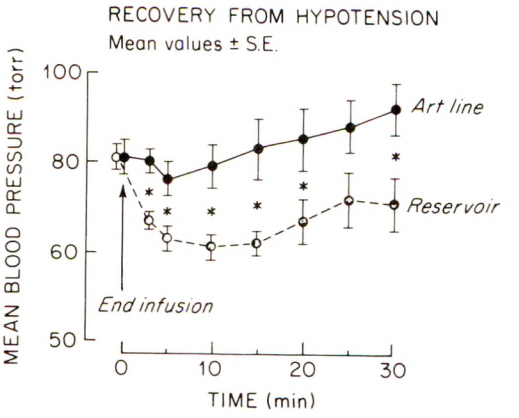


FIG 3. Mean values (± SE) for blood pressure recovery after cryptenamine infusion. Scales are as in fig 2, except that time 0 here marks the end of the drug infusion. Blood pressures in group 1 continued to fall even after the infusion was ended, and ran 10 to 20 torr lower than in group 2 throughout the recovery period.

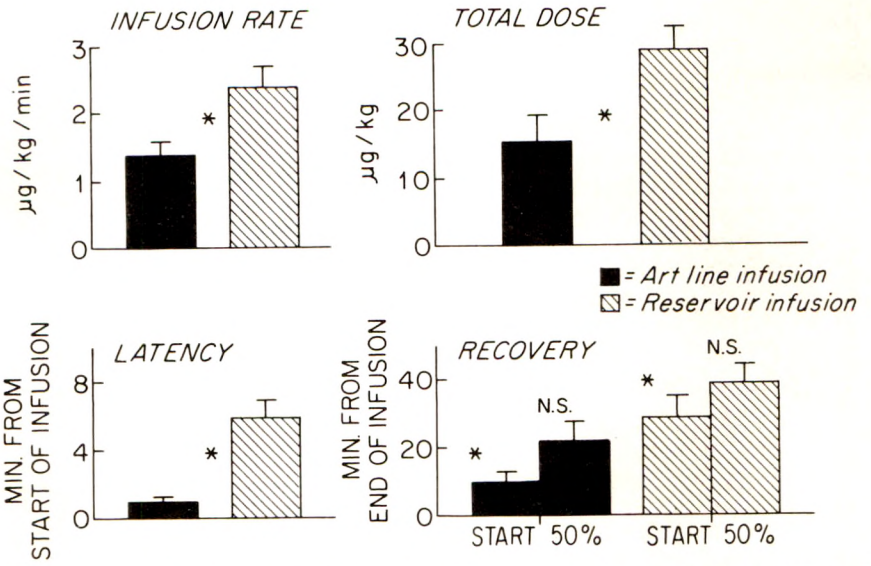


FIG 4. Comparison of infusion rate, total drug dose, latency, and recovery in the 2 groups of patients. Fifty percent recovery time is the time when the blood pressure had returned to 50 percent of control values.

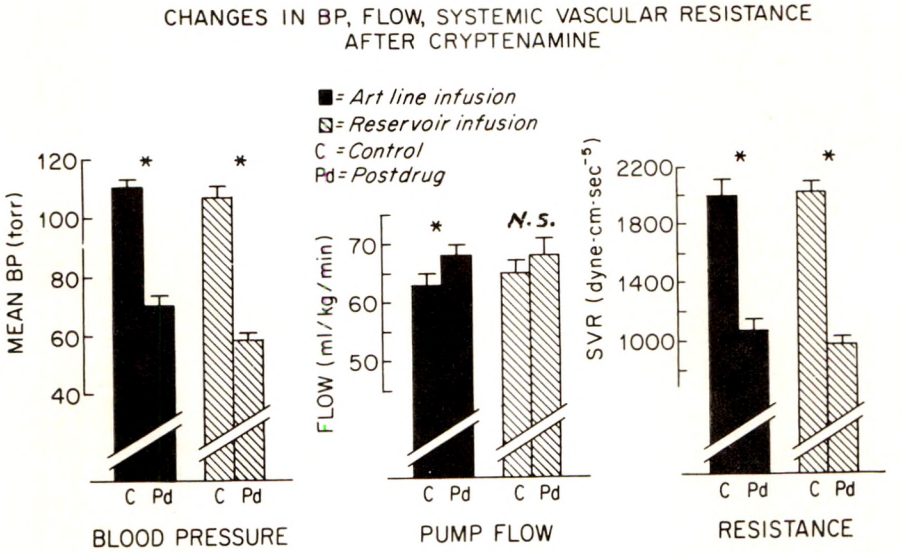


FIG 5. Mean values (± SE) for blood pressure, pump flow, and calculated systemic vascular resistance before and after cryptenamine. Bars for group 1 values are cross hatched; group 2 values are shown by plain bars. Control measurements were made just before drug infusion was started. Postdrug (Pd) blood pressures and resistances are means of the lowest values reached in each patient at any time after start of drug infusion. Postdrug flows are means of average pump flows during drug infusion.

the lower total dose and infusion rate, shorter latency, and faster recovery in patients who received cryptenamine in the arterial line (group 2). The values differ significantly between the 2 groups, except for the 50 percent recovery times, which scatter widely in both groups. (These data were often difficult to obtain, as the times often coincided with defibrillation, weaning from the pump, infusion of pump prime, etc.)

Means of individual changes in pressure, pump flow, and calculated systemic vascular resistance are shown in fig 5. The pressures used to calculate these means were those immediately prior to the start of infusion (labeled "control" in the table), and the *lowest* pressure reached (even transiently) in a given patient at any time after the start of infusion. Average pressures during infusion, of course, ran higher (see table). In

group 1, 3 of the 10 patients were given bolus injections of 0.1 mg phenylephrine when pressure seemed temporarily too low. This was never necessary in group 2. Mean pump flows in both groups before cryptenamine were 63 to 64 ml/kg/min (which in most cases had been cut back from at least 70 ml/kg/min, in an effort to control the rising pressure prior to drug infusion). After cryptenamine, increases in pump flow were again possible because of the profound drop in vascular resistance brought about by the drug (fig 5).

At the conclusion of the bypass periods, all hearts were rewarmed and electrically defibrillated without difficulty. Four of the 18 patients were given 1 dose of atropine (1 to 1.2 mg into the reservoir) as treatment for bradycardia occurring just after defibrillation. This alleviated the bradycardia in every case. No other arrhythmias were seen. All patients came off the pump easily (mean separation time was 1.9 ± 0.4 minutes), appeared to be vasodilated, and tolerated transfusion of the remaining pump prime. The mean of the patients' central venous pressures after infusion of the residual volume in the oxygenator was 9.4 torr (range 6 to 14 torr). Mean of the integrated mean blood pressures at this time (approximately 5 minutes after coming off the pump) was 94 torr (range 67 to 110 torr). Positive inotropic agents were not needed. With 1 exception, all patients recovered uneventfully. Patient No. 10, who died on the 1st postoperative day, had poor distal coronary vessels and was re-explored 12 hours postoperatively for bleeding. It was not felt that his demise was related to cryptenamine.

DISCUSSION

The results reported show that it is indeed possible to lower peripheral vascular resistance and thus blood pressure during cardiopulmonary bypass by a drug acting on afferent pressure regulating receptors, even though blood flow to some of the receptor areas involved (heart, lungs) may be greatly reduced or even transiently interrupted. This is in keeping with our recent demonstration in dogs[15] that local application of minute amounts of hypotensive veratrum alkaloids to 1 carotid sinus only caused marked and prolonged hypotension. The efficacy of this type of drug therapy during extracorporeal perfusion also implies that peripheral vascular resistance in this situation is largely, if not entirely, under neurogenic control, because it is well established that these drugs possess no direct vasodilator action, but rather act to lower blood pressure by a decrease in efferent neurogenic vasoconstrictor as well as cardiac sympathetic tone.[16] This is emphasized because there is some evidence for the involvement of humoral vasoactive agents during bypass.[12,13,17] Nevertheless, the fact that in this series all 18 patients responded to a drug known to act neurogenically (via sensory receptors) implies that humoral factors play only a minor role or occur only in certain patients, or that the humoral mechanisms are closely linked to neurogenic ones. The latter is, of course, true for the renin-angiotensin system.

In this study, the infusion rate required was titrated carefully in each patient; we always started with a rate expected to be below threshold. (This fact accounts in part for the observed latencies, which would have been lower had we begun with higher infusion rates.) With growing experience and with infusion into the arterial line, it should be possible to start with a higher rate of infusion and thus reduce further the latency between start of infusion and onset of pressure fall.

The markedly longer latency, even at higher infusion rates, and the greater total drug doses required when the drug was given into the oxygenator reservoir were expected. The onset and magnitude of any drug effect are related to the drug concentration in the receptor areas, in this case the areas where pressure-regulating sensory receptors are located. The blood concentration of cryptenamine in the group 2 patients could be easily calculated from the rate of infusion and the blood flow through the arterial line (pump output). It is to be expected from the high lipid solubility of these alkaloids,[9] and has indeed been observed in animal experiments, that access of the drug to the receptors from the capillary vascular bed is rapid, and that the virtual volume of distribution increases greatly with the 1st passage of the drug through the capillary bed. Hence, the 1st circulation yields the highest drug concentrations in the biophase.

A similar calculation was not as easy when the drug was infused into the reservoir. Although the blood volume in the reservoir was recorded (between 400 ml and 1500 ml), this did not remain constant during the infusion. Furthermore, the degree of mixing in the reservoir may be variable,

and any estimate of the drug concentration in the arterial blood is thus subject to considerable uncertainty. This seems to be borne out by the results; the latency varied from 0.5 to 14 minutes. (Of course, the drug effect is not determined solely by the blood or tissue concentration; there must be, for example, some variability in sensitivity between individual patients.) It is also obvious that some degree of "filling up" must have occurred, as indicated by the sometimes considerable period of "overshoot" in group 1 patients after discontinuation of the infusion.

The seriousness with which anesthesiologists and surgeons view hypertension during and after open heart operations is attested to by the number of recent publications dealing with its treatment,[3-5,18,19] including 1 advocating the use of epidural anesthesia.[20] One of the most popular methods currently used consists of the infusion of sodium nitroprusside[21,22] or nitroglycerin.[23] This approach may well be accompanied by a reflex increase in cardiac sympathetic tone and hence cardiac metabolic demands. Such a reflex increase in heart rate and contractility during carotid sinus hypotension is well documented.[7,24] In man, increased heart rate and myocardial contractility have been seen after nitroglycerin.[8] A coronary vasoconstrictor component in response to the baroreceptor stimulus has also been demonstrated, although it is normally overwhelmed by metabolically induced coronary vasodilatation.[7] Conversely, stimulation of the carotid sinus nerves[25]—which is quite similar to drug-induced stimulation—and injection of veratrum alkaloids into the coronary circulation[26] cause the opposite effects: decreased cardiac load and decrease in coronary resistance.

It is to be remembered, of course, that reflex effects may be attenuated, blocked, or even reversed by CNS depressants, especially general anesthetic agents. However, our patients received no general anesthetic during the bypass period (see Methods); and it has been shown in animals that even high doses of morphine do not depress baroreceptor reflex activity.[27] There is, to our knowledge, no systematic information available concerning central blocking of reflex responses by general anesthetic agents. It seems to us, therefore, that the rationale for using a drug with a mechanism of action like cryptenamine is sound. The drug not only lowers the cardiac load by reducing arterial pressure, but also can be expected to reduce cardiac sympathetic nervous tone. It may well also promote coronary vasodilatation.[26]

No adverse responses to the infusion of the drug were seen, with the possible exception of bradycardia in 4 patients immediately following cardioversion. In view of the fact that bradycardia at that time is not uncommon and may be caused by a number of factors (eg, mechanical, coronary air embolism, inadequate warming, and others), this observation cannot be attributed with any certainty to the drug. At any rate, it was easily controlled by atropine.

The series reported here is too small to permit valid comparison of clinical outcome. Yet, all patients did well clinically (with the 1 exception described under Results). They were vasodilated, and cardioversion and separation from the pump were quick and easy. The main difficulty encountered was the adjustment of the infusion rate. This problem was less in the group 2 patients and was alleviated with experience. Nevertheless, it would be desirable to have a shorter-acting alkaloid available. On the other hand, any drug acting as cryptenamine does by reducing sympathetic nervous outflow (and increasing vagal tone) has a physiological "bottom" below which neurogenic tone cannot be reduced.[28]

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Chest radiographs were examined to study 80 attempts in 41 patients (15 tracheostomy, 26 orotracheal tube) at placing suction catheters in the left main bronchus. In patients with tracheostomy the success rate was 75 percent using an angled catheter, 10 percent with a straight catheter. The success rate was 20 percent (angled) and 15 percent (straight) in patients with orotracheal tubes. *(Scott AA, Sandham G, Rebuck AS: Selective tracheobronchial aspiration. Thorax 32:346-348, 1977)*

Anesth Analg
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Characteristics of Succinylcholine Neuromuscular Blockade in Neonates

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The neuromuscular response of 10 infants to train-of-four electrical stimuli was examined during anesthesia with N_2O-O_2-halothane and after 1.5 mg/kg of succinylcholine IV. The ulnar nerve was stimulated electrically with a Grass S88 SIU at the wrist; the resultant force of thumb adduction was recorded. Trains-of-four, 2-Hz, supramaximal, square stimulating pulses (0.1 m/sec) were applied every 12 seconds. The maximum twitch depression following injection of succinylcholine and the train-of-four ratio were noted for the control period, at 25 percent neuromuscular transmission (T_{25}), 50 percent neuromuscular transmission (T_{50}), and 90 percent transmission (T_{90}). The degree of neuromuscular blockade following succinylcholine was calculated by comparing the height of the 1st twitch of the train of stimuli to the height of the 1st twitch of the train of stimuli during anesthesia alone.

During anesthesia and before administration of succinylcholine the train-of-four ratio averaged 0.92, a ratio comparable to that reported in adults during similar anesthesia. The average maximum neuromuscular blockade after 1.5 mg/kg succinylcholine was 91.1 percent. At T_{25} the train-of-four ratio averaged 0.72; at T_{50} the ratio averaged 0.79; and at T_{90} the ratio averaged 0.87. Using the criteria for succinylcholine phase II neuromuscular block suggested by Lee, no infant developed a phase II block with an initial dose of succinylcholine of 1.5 mg/kg.

Key Words—NEUROMUSCULAR RELAXANTS, succinylcholine. ANESTHESIA, pediatric.

NEONATES require more depolarizing neuromuscular relaxants such as decamethonium[1] and succinylcholine[2-4] on a weight basis than do adults to achieve equal neuromuscular blockade. The initial characteristics of the neuromuscular blockade with depolarizing relaxants may also differ between infants and adults. For example, Churchill-Davidson and Wise[1] noted many characteristics of a phase II block in neonates following a paralyzing dose of decamethonium. They suggested that neonates develop a phase II block following an initial dose of succinylcholine. Wylie and Churchill-Davidson further suggested that neonates would have slightly prolonged neuromuscular blockade as compared to adults because of the phase II block.[5] However, neither of these hypotheses was documented.

Since gross fasciculations are rarely seen in neonates following succinylcholine administration and since pseudocholinesterase levels in neonates are about one-half those of the adult,[6] we wondered if the neonate had an initial phase II block following a paralyzing dose of succinylcholine. Lee[7] recently characterized phase I and phase II of neuromuscular block in adult man following succinylcholine on the basis of train-of-four ratios (the ratio of the height of the 4th twitch response to the height of the 1st twitch response during application of 4

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2-Hz supramaximal square-wave stimuli of 0.1 m/sec).

By avoiding tetanic stimulation, the nature of neuromuscular blockade can be assessed as often as every 12 seconds.[6-8] During phase I block the train-of-four ratios were high, ie, 0.7 to 0.9; during phase II block they were low, ie, 0.3 or less. After a total dose of 3 to 5 mg/kg of succinylcholine, phase II block was evident in all patients studied by Lee during halothane anesthesia. The transition from phase I to phase II block was abrupt as the total dose of succinylcholine increased. The transition in an individual adult occurred with an increase in the total dose of succinylcholine of 1 to 2 mg/kg.

The present study defines in neonates the characteristics of neuromuscular blockade following a paralyzing dose of succinylcholine (1.5 mg/kg) using train-of-four criteria.

METHODS AND MATERIAL

Ten infants, born at or near term, having operations requiring general endotracheal anesthesia were studied. None had electrolyte disturbances nor apparent volume deficiencies. The age and weight of each infant are recorded in the table.

Atropine (0.03 mg/kg) was given IM 30 minutes prior to induction of anesthesia. Anesthesia was induced and maintained with N_2O-O_2-halothane for the duration of the study. Inspired concentrations of halothane during the study ranged from 1.5 to 2.0 percent. Neither the alveolar levels of halothane nor arterial blood gases were measured. However, respiration was assisted or controlled as necessary in an attempt to maintain eucarbia. All patients were eurthermic at the time of the study.

The neuromuscular blocking effects of succinylcholine were monitored in a standard way by stimulating the ulnar nerve and recording the twitch height.[8-10] Sterile 25-gauge metal needles were placed subcutaneously close to the ulnar nerve at the wrist. Trains-of-four, 2 Hz, supramaximal, square stimulating pulses (0.1 m/sec) were applied every 12 seconds from a Grass S88 stimulation isolation unit. A Grass FT-03 force-displacement transducer connected to a string with fixed tension was secured to the thumb by means of a small wooden applicator. The forearm was taped to a special armboard at the fingers, wrist, and mid-forearm to prevent rotation of the hand. The transducer was aligned parallel to the fully abducted thumb. The electrical signal resulting from thumb adduction was amplified and recorded on a Hewlett-Packard paper recorder.

After stabilization of the twitch height and after IV atropine (0.1 mg), succinyl-

TABLE
Train-of-Four Ratios in Anesthetized Neonates
Before and After 1.5 mg/kg Succinylcholine

Patient	Weight	Age (Days)	Ratio before relaxant	Ratio after succinylcholine		
				T_{25}*	T_{50}*	T_{90}*
1	3.5	1	1.03	0.73	0.82	0.88
2	3.8	6	1.06	0.61	0.88	0.95
3	2.5	10	0.87	0.79	0.88	0.95
4	3.1	14	0.67	0.40	0.50	0.50
5	3.8	1	0.96	0.64	0.83	1.00
6	3.3	3	0.96	1.00	0.98	0.95
7	2.3	1	0.79	0.63	0.75	0.77
8	3.1	1	1.00	1.00	0.83	0.91
9	4.0	30	1.00	0.80	0.85	0.94
10	3.2	28	1.00	0.64	0.79	0.90
Mean ± SD	3.3 ± 0.9	9.5 ± 11.2	0.92 ± 0.20	0.72 ± 0.18†	0.79 ± 0.22†	0.87 ± 0.15†

*T_{25}, T_{50}, and T_{90} represent 25, 50, and 90 percent neuromuscular transmission, respectively.
†$p<0.50$ when compared to control ratio.

choline (1.5 mg/kg) was administered IV. Succinylcholine was diluted with normal saline to 1.0 mg/ml. The maximum twitch depression following injection of succinylcholine and the train-of-four ratio were noted for the control period, at 25 percent neuromuscular transmission (T25, 75 percent neuromuscular blockade), at 50 percent neuromuscular transmission (T50, 50 percent neuromuscular blockade), and at 90 percent neuromuscular transmission (T90, 10 percent neuromuscular blockade) from the paper recording. The degree of neuromuscular blockade following succinylcholine was calculated by comparing the height of the 1st twitch of the train of stimuli to the height of the 1st twitch of the train of stimuli during anesthesia alone.

RESULTS

The average maximum neuromuscular blockade after 1.5 mg/kg succinylcholine was 91.1 percent (± 8.5 SD). Before administration of succinylcholine the train-of-four ratio during anesthesia averaged 0.92, at T25 the ratio averaged 0.72, at T50 the ratio averaged 0.79, and at T90 the ratio averaged 0.87 (table). Unpaired Student's *t*-tests showed no statistical difference between the control train-of-four ratios and those at T25, T50, or T90 ($p<0.50$).

DISCUSSION

Unanesthetized infants in the 1st month of life appear to have less neuromuscular reserve during tetanic stimulation than do adults.[1,11] In these neonates there is no fade of twitch height with repetitive stimulation rates of 1 to 2 Hz but at 20 Hz there is significant fade of twitch height. Premature infants may have posttetanic exhaustion lasting 15 to 20 minutes. Older infants and adults exhibit no fade of twitch height with high-frequency stimuli.

In the present study, the train-of-four ratio during N_2O-O_2-halothane averaged 0.92. This decrease in train-of-four ratio during halothane anesthesia in infants is comparable to that reported in adults by Ali et al[8] and Lee[7] during halothane anesthesia. By the train-of-four criteria for succinylcholine phase II block described by Lee,[7] neonates have a phase I block following 1.5 mg/kg succinylcholine, as do adults.[7,9,12] Since neonates may have profound bradycardia with repeated doses of succinylcholine,[13] we did not challenge our patients with repeated doses of succinylcholine to determine at what total dose (mg/kg) a phase II block develops.

The absence of gross fasciculations in neonates with a paralyzing dose of succinylcholine is not related to initial development of a phase II block. Fine fasciculations of fingers and a brief increase in recording baseline are often seen following IV succinylcholine. Most likely the absence of gross fasciculations is related to dilution of succinylcholine in a large extracellular fluid volume prior to its distribution to a relatively small muscle mass. Extracellular fluid volume is about 45 percent of body weight in the newborn, 30 percent at 2 months of age, 20 percent at 4 to 6 years of age, and 16 percent in adults. The muscle mass of an infant is 20 to 25 percent of body weight; an adult's muscle mass is 40 to 50 percent of body weight.[14,15] Furthermore, at equipotent initial doses of succinylcholine, neonates do not have significantly prolonged recovery times when compared to older children.[16]

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Experimental subarachnoid hemorrhage (SAH) in dogs was produced by introducing blood into the subarachnoid space through a catheter connected to an artery of the animal. Intact animals and those with preserved vagi and heart sympathetic innervation developed rapid onset of arrhythmias which correlated with the sudden increase in intracranial pressure. Animals with sections of both vagi and heart sympathetic innervation, but with an intact spinal cord, developed arrhythmias that were delayed in onset and did not correlate with the changes in intracranial pressure. These arrhythmias were preceded by changes in the QT interval, T wave, and ST segment. It was concluded that the arrhythmias could be produced either by direct autonomic discharges to the heart or by increased circulating and tissue catecholamines. The clinical implications of these findings are discussed. *(Estanol BV, Loyo MV, Humberto Mateos JH, et al: Cardiac arrhythmias in experimental subarachnoid hemorrhage. Stroke 8:440-447, 1977)*

Laboratory Evaluation of Pressure Transducer Domes Containing a Diaphragm

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Pressure transducers are being used with increasing frequency in patient care. The recent availability of sterile transducer domes containing a diaphragm provides a means for reducing the risk of bacteremia when using these devices. The present studies measured the effect of diaphragm domes on the accuracy of pressure measurement. The sensitivity and frequency responses of 5 pressure transducers utilizing diaphragm and nondiaphragm domes were compared. The results indicate that the type of dome utilized and the method of dome application can significantly modify pressure transducer performance. The data are useful in providing optimal accuracy and reliability of pressure measurments when using a diaphragm dome, pressure transducer combination.

Key Words — EQUIPMENT, transducers. MEASUREMENT TECHNIQUES, transducers.

MEASUREMENTS of arterial and venous pressure have become essential components of sophisticated patient care. The transducers which are widely used in making these measurements may be a source of bacteriologic contamination of the bloodstream.[1-3] Therefore, it is essential that the transducer dome, ie, the fluid-filled chamber in continuity with the patient's bloodstream, be sterile.

Recently, an improvement in transducer dome design has become available from a number of manufacturers. The difference between these new domes and those used previously is the addition of a diaphragm within the fluid-filled chamber (fig 1). The purpose of this diaphragm is to bacteriologically isolate the sterile fluid chamber from the proximal portion of the dome, which is attached to a nonsterile transducer.

Since diaphragm domes are supplied sterile and intended for single patient use only, they have the advantage of minimizing bacteriologic contamination of the patient from transducers. The presence of the diaphragm introduces the potential disadvantage of significantly altering the static and/or dynamic accuracy of the pressure transducer

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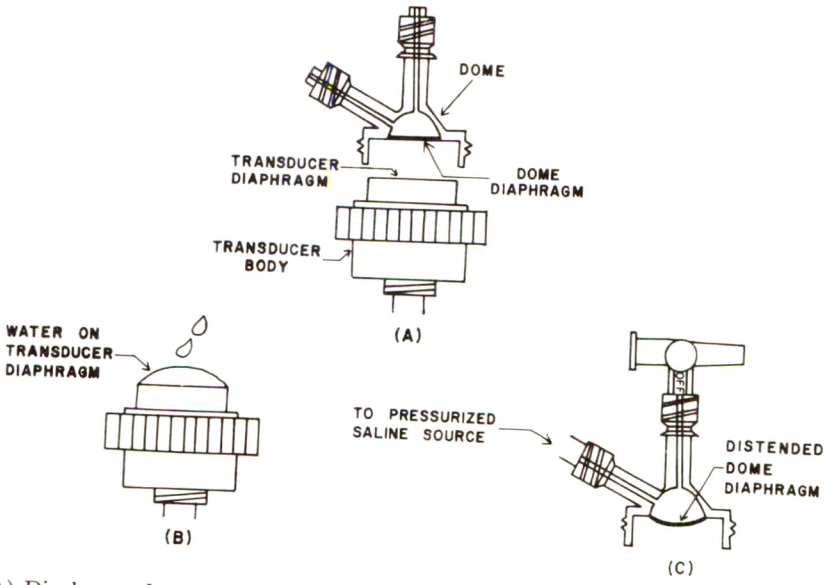


FIG 1. (A) Diaphragm dome and pressure transducer. (B) Application of water to transducer diaphragm. (C) Distention of dome diaphragm by application of pressurized saline.

and thereby altering the accuracy of the pressure measurement system. Transducer sensitivity, that is, the output voltage generated in response to a *constant* pressure, is one factor affecting overall *static* accuracy. Transducer frequency response, that is, the output voltage generated in response to a *sinusoidally varying* pressure of a *range of frequencies,* is one factor affecting overall *dynamic* accuracy.

The studies to be described evaluated the sensitivity and frequency response of pressure transducers fitted with diaphragm transducer domes. These characteristics were selected because they are important in accurate pressure measurement and potentially affected by the presence of the diaphragm. To provide reliable pressure measurements, these functional characteristics must be within prescribed limits. Measurements using conventional nondiaphragm domes were used to provide the reference values for comparison with similar values obtained with diaphragm domes attached to the same transducer. Pressure transducers in widespread hospital use were selected for these studies.

METHODS

A total of 1,185 measurements was made. Of these, 825 measured transducer sensitivity and 330 measured transducer frequency response. The remaining 30 measurements quantified the diaphragm rupture pressure for the diaphragm domes tested.

Five transducers and 10 kinds of domes were studied. Table 1 identifies the nondiaphragm and diaphragm domes, and the corresponding transducers with which each was tested.

Twenty-five measurements of sensitivity and 10 measurements of frequency response were performed with each nondiaphragm dome, transducer combination (table 1). The sensitivity measurements were divided into 5 groups of 5 measurements each. Each

TABLE 1
Transducer and Dome Combinations Studied

Transducer	Dome	
	Nondiaphragm	Diaphragm
Statham, P23Db†	TA1009†	TA1009D†
		D-250*
Statham, P23Ia†	TA1009†	TA1009D†
		D-250*
Statham, P23ID†	TA1010†	TA1010D†
Bell & Howell, 4-327I	P/N368444	P/N368787-0100
Bentley-Trantec, 800	D-210	D-240

*Diaphragm domes manufactured by Bentley-Trantec for use with corresponding Statham transducers. Bell & Howell, CEC Division, Pasadena, California. Bentley Laboratories, Irvine, California

†Gould, Inc., Measurement Systems Division, Oxnard, California

group of 5 measurements was performed using a new nondiaphragm dome attached to the transducer as recommended by the manufacturer. Between successive measurements in each group, the transducer dome was removed and then replaced on the transducer. The frequency-response measurements were divided into 5 groups of 2 measurements each. Each group of 2 measurements was performed utilizing a different nondiaphragm dome from the ones which had been used for sensitivity testing. The dome was removed and then replaced on the transducer between successive frequency-response measurements also.

The sensitivity and frequency-response measurements for each diaphragm dome were carried out in similar manner, except that both groups of measurements were performed with each dome placed on the transducer using each of 4 different application technics. With diaphragm domes, physical contact between the dome diaphragm and the pressure-sensitive transducer diaphragm is an important contributing factor in sensitivity and frequency-response characteristics. The different application technics used for attaching the diaphragm domes to the transducer were (1) the interposition of water between the dome diaphragm and the transducer diaphragm; (2) distending the dome diaphragm by the injection of saline; (3) the use of both water and pressure distention of the dome diaphragm; and (4) direct approximation of a dry dome diaphragm with a dry transducer diaphragm. The technic for interposing water between the dome diaphragm and transducer diaphragm was as follows: While holding the transducer body vertically, 4 or 5 drops of water were applied to the transducer surface; the dome was then carefully attached, trapping part of this water between the diaphragm surfaces. Pressure distention of the dome diaphragm was accomplished by filling the dome with saline and maintaining a pressure of approximately 50 torr from a fluid reservoir hanging 27 inches above the dome as it was attached to the transducer.

These four technics for application of the diaphragm domes were selected either because they are recommended by the dome manufacturer or because they are deviations from the recommended technic which might occur in the clinical situation. The direct approximation technic is the easiest to use, and therefore likely to occur, although it is not recommended by any manufacturer. The use of both water and pressure distention is the most cumbersome to use and is recommended by 2 manufacturers. Pressure distention only is recommended by 1 manufacturer. The results of these studies, therefore, quantitate the effects of deviations from recommended technic as well as the effect of the dome diaphragm when used with the recommended technic. Thus, 7 diaphragm-dome combinations (table 1) with each of 4 different application technics were studied. In each of these 28 studies, 5 groups of 5 sensitivity measurements each and 5 groups of 2 frequency response measurements each were carried out for a total of 700 sensitivity measurements and 280 frequency-response measurements.

Transducer sensitivity was measured as the output voltage resulting from the application of 200 torr pressure and an excitation voltage of 7.5 volts dc. Output voltage was measured with a Fluke,* model 893A, ac-dc differential voltmeter. Pressurization of the test transducer-dome combinations was carried out by the application of air from a sphygmomanometer bulb and quantified with a Wallace and Tiernan,† model 62B-2A-005D, pressure gauge. Transducer excitation voltage was delivered from a Power Design,‡ model 2005A, precision power supply and also quantified with the Fluke voltmeter. The overall accuracy of this test system is 0.5 percent.

Transducer frequency responses were determined using the methodology of McCutcheon, Evans, and Stanifer.[4] Briefly, this technic involves the oscilloscopic measurement of transducer output voltage resulting from the application of a sinusoidally varying pressure over a range of frequencies. The amplitude of the pressure sinusoid was 20 torr peak-to-peak, and the frequency ranged between 0 and 1000 Hz. Figure 2(A) is a photograph of a typical frequency-response curve as observed on the oscilloscope. With increasing frequency, the amplitude of the transducer output remains relatively constant until a point at which it begins to rise rapidly, peaks, and then declines.

The frequency corresponding to peak transducer output is the resonant frequency,

*John Fluke Manufacturing Co., Inc., Seattle, Washington

†Penwalt Corporation, Wallace and Tiernan Division, Belleville, New Jersey

‡Power Design Inc., Westbury, New York

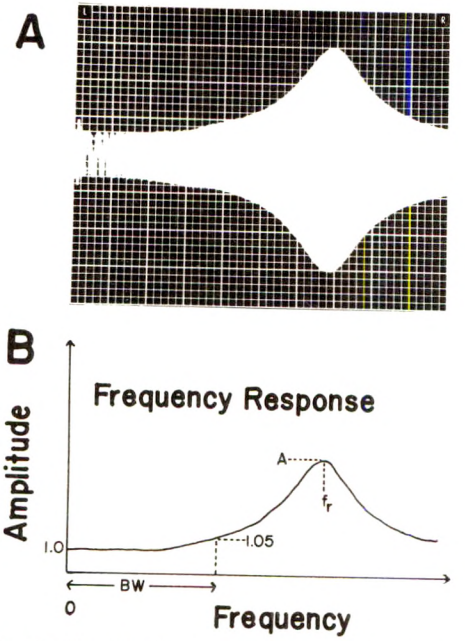


FIG 2. (A) Oscilloscope photograph of representative transducer frequency response. (B) Relationship of bandwidth (BW) to resonant frequency (f_r) and the ratio (A) of transducer output amplitude at f_r to transducer output at 0 frequency.

f_r. The range of frequencies, beginning at 0, over which transducer output remains constant within 5.0 percent is the bandwidth, *BW*. In the present studies transducer bandwidths were calculated from the equation:[5]

$$BW = f_r\sqrt{1 - \frac{\sqrt{\left(\frac{A}{1.05}\right)^2 - 1}}{A^2 - 1}}$$

where A is the ratio of transducer output at f_r to transducer output at 0 frequency. Figure 2(B) illustrates these interrelationships. A Millar,* model MPG-30, multifunction generator and chamber, and a Wavetek,† model 144, sweep oscillator were used to produce the sinusoidal pressure. In these studies, the test dome was applied to the transducer and directly coupled to the pressure chamber of the Millar instrument. Sinusoidally varying pressure was then applied to the transducer and the frequency adjusted until peak transducer output was obtained. The frequency producing peak transducer output and the magnitude of this output were determined. Transducer output was measured with a Tektronix‡ oscilloscope system including a model 5103N main frame, a model 5A18N dual trace amplifier, and a model 5B12N time base. Frequency was measured with a Hewlett Packard,§ model 5302A, universal counter.

The pressure required to rupture the unsupported diaphragm of each diaphragm dome unit used in the sensitivity and frequency-response measurements was determined. In addition, 5 new Bell and Howell 368787-0100 diaphragm domes were tested. Pressure was quantitated with a U. S. Gauge,‖ model P602, pressure gauge.

RESULTS

The results of the transducer sensitivity tests are included in table 2. Each value is the mean (±1 SD) of 25 determinations. Each determination represents the transducer output voltage change in millivolts resulting from the application of 200 torr test pressure. The sensitivity specified by the manufacturer for each of the 5 test transducers is 5 ± 0.05μ v transducer output, per 1 volt of excitation, per 1 torr of applied pressure. Thus with an excitation of 7.5 volts, the transducer output voltage change produced by the application of 200 torr test pressure should have been 7.50 ± 0.075 mv.

It is apparent that the output voltage for each transducer when used with a nondiaphragm dome closely approximated the specified value. Further, the reproducibility of these groups of measurements, as shown by the small SD values, was excellent. Thus with nondiaphragm domes, the influence of repeated dome applications and sensitivity measurements does not appear to be significant.

In contrast, with diaphragm domes the technic of application is a critical determinant of transducer sensitivity. This conclusion is supported by the observations that mean transducer output values and the variability about these mean values changed widely with the technic of application. Additionally, the technic of application recommended by the manufacturer did not necessarily result in the most reliable sensitivity or produce minimum variability. For example, fitting the Statham P23Db transducer with a Statham TA1009D dome, using pressurization only as recommended, resulted in a mean output of 7.87 mv with a SD of 0.21

*Millar Instruments, Inc., Houston, Texas

†Wavetek, San Diego, California

‡Tektronix Inc., Beaverton, Oregon

§Hewlett Packard, Palo Alto, California

‖U. S. Gauge, Sellersville, Pennsylvania

TABLE 2

Transducer Sensitivity Values for Nondiaphragm Domes and Diaphragm Domes Applied with Each of 4 Technics (Ideal value 7.50 mv)

Transducer and dome tested	Mean sensitivity (1 SD) in mv/200 torr pressure				
	Nondiaphragm dome	Diaphragm dome			
		Application technic			
		W	P	W/P	N
Statham, P23Db, TA1009	7.51 (0.02)				
TA1009D		7.49 (0.10)	7.87 (0.21)	7.60 (0.18)	7.58 (0.17)
D-250		7.46 (0.10)	7.60 (0.03)	7.56 (0.03)	7.42 (0.09)
Statham, P23Ia, TA1009	7.51 (0.01)				
TA1009D		7.24 (0.41)	7.51 (0.13)*	7.26 (0.37)	7.27 (0.28)*
D-250		7.39 (0.27)	5.16 (0.26)	7.44 (0.23)	5.41 (0.30)
Statham, P23ID, TA1010	7.51 (0.01)				
TA1010D		7.44 (0.06)	7.55 (0.02)	7.48 (0.02)	7.54 (0.05)
Bell & Howell, 4-327I, P/N368444	7.55 (0.01)				
P/N368787-0100		7.56 (0.02)	7.56 (0.01)	7.57 (0.01)	7.56 (0.01)
Bentley-Trantec, 800, D-210	7.54 (0.01)				
D-240		7.48 (0.21)	7.67 (0.06)	7.52 (0.03)	7.39 (0.04)

W = Water between dome and transducer diaphragms

P = Pressure distention of dome diaphragm

W/P = Both water and pressurization

N = Neither water nor pressurization

* = Insertion of neoprene disc between dome and transducer diaphragms

n for each value equals 25

Underscore indicates method of application recommended by dome manufacturer

mv. The mean value of the output for this same combination using water only was 7.49 mv with a SD of 0.10 mv.

From the point of view of clinical application, the calculated percentage error of the mean sensitivity and the percentage error of 1 SD with respect to the 7.50 mv ideal value, as shown in table 3, may be more useful. Again, error and variability of this error were minimal with nondiaphragm domes, but significant with some technics of application of diaphragm domes. For example, in measuring a pressure of 100 torr, with the Statham P23Db transducer and TA1009D dome applied with pressurization only as recommended, the mean error from this source alone would be 4.9 torr with a SD of 2.9 torr.

The results of the transducer frequency-response tests are included in table 4. The larger number in each pair is that frequency corresponding to peak transducer output (resonant frequency). The smaller number is the ratio of the transducer output at the resonant frequency to the transducer output at zero frequency. With respect to the clinical measurement of arterial pressure for heart rates up to 120 beats/min, the pressure measurement system should have a frequency response which is flat within 5 percent to 20 Hz,[6] ie, must have a bandwidth of 20 Hz. The larger the output at resonance, the smaller the fraction of the resonant frequency for which the frequency response will be flat, ie, for a given resonant frequency, the larger the amplitude at resonance, the smaller the bandwidth. On the other hand, the higher the resonant frequency, the less important the amplitude at resonance. Table 5 contains the bandwidth values calculated from the data in table 4.

As can be seen from table 5, there was considerable variability in the transducer bandwidth measurements. This was true both between transducers fitted with nondiaphragm domes, and for a given transducer with respect to the various technics for applying the diaphragm domes. The variability between transducers can be attributed to differences in the size and stiffness of the transducer diaphragm. The variability for a given transducer illustrates again the importance of the technic of dome application. Importantly, although there were variations introduced by the various application technics for a given transducer-dome combination, all but 3 were acceptable. The exceptions, because they fell below the 20-Hz value, were the 12.2- and 12.8-Hz values measured with the Statham P23Ia transducer and the Bentley-Trantec D250 dome applied without water, and the 14.8 Hz value measured with the Bell and Howell 4-327I transducer with the Bell and Howell 368787-0100 dome applied without water or pressurization.

The results of the diaphragm-dome rupture-pressure tests are shown in table 6. It is apparent that, with the exception of the used Bell and Howell 368787-0100 domes, in which the diaphragm ruptured with a pressure as low as 150 torr, the rupture pressure was consistently in excess of pressures encountered in the usual clinical situation. The rupture pressure of the new Bell and Howell domes was at least 500 torr.

COMMENT

The present studies present new evidence describing the sensitivity and frequency-response characteristics of diaphragm transducer domes and quantitate the pressure required to rupture the diaphragm in these devices.

Transducer sensitivity was influenced by the type of dome used and the method of application. For each of the transducer, nondiaphragm dome combinations tested, the percentage error in sensitivity was less than the 1 percent specified by the manufacturers. In contrast, there was no transducer, diaphragm dome combination which exhibited less than 1 percent error for *all* technics of application (tables 2 and 3). However, with 3 of the 7 combinations, at least 1 technic of application resulted in less than 1 percent error in sensitivity. In 3 of the remaining 4, there was at least 1 application technic which resulted in less than 2 percent error in sensitivity. The variability in sensitivity with the Statham P23Ia transducer and Bentley-Trantec D250 dome ranged between 3 and 4 percent (table 3). In our opinion, this degree of variability is unacceptable. With the Bell and Howell transducer, the change in the sensitivity error from the nondiaphragm dome to the diaphragm dome applied by any technic was less than 1 percent.

In the clinical situation, a total inaccuracy in pressure measurement of 5 percent may be acceptable.[7] This total inaccuracy is the accumulation of contributions from static and dynamic factors. Since transducer sensitivity error is only 1 of the components

TABLE 3
Percent Error of Transducer Sensitivity Values for Nondiaphragm Domes and Diaphragm Domes Applied with Each of 4 Technics

Transducer and dome tested	Percent error of mean sensitivity (percent error of 1 SD)				
	Nondiaphragm dome	Diaphragm dome			
		Application technic			
		W†	P	W/P	N
Statham, P23Db, TA1009	0.2 (0.2)				
TA1009D		−0.1 (1.4)	4.9 (2.9)	1.4 (2.4)	1.1 (2.3)
D-250		−0.6 (1.3)	1.3 (0.4)	0.8 (0.4)	−1.1 (1.2)
Statham, P23Ia, TA1009	0.1 (0.2)				
TA1009D		−3.4 (5.5)	0.1 (1.7)*	−3.3 (5.0)	−3.0 (3.8)*
D-250		−1.4 (3.6)	−31 (3.5)	−0.8 (3.0)	−28 (4.0)
Statham, P23ID, TA1010	0.1 (0.1)				
TA1010D		−0.7 (0.8)	0.7 (0.3)	−0.3 (0.3)	0.6 (0.7)
Bell & Howell, 4-327I, P/N368444	0.7 (0.1)				
P/N368787-0100		0.8 (0.2)	0.8 (0.1)	1.0 (0.2)	0.9 (0.2)
Bentley-Trantec, 800, D-210	0.6 (0.1)				
D-240		−0.3 (2.9)	2.2 (0.8)	0.3 (0.5)	−1.5 (0.5)

†See footnotes to table 2 for explanation of abbreviations

TABLE 4
Resonant Frequency and Amplitude at Resonance for Nondiaphragm Domes and Diaphragm Domes Applied with Each of 4 Technics

Transducer and dome tested	Resonant frequency, Hz (relative amplitude at resonance)				
	Nondiaphragm dome	Diaphragm dome			
		Application technic			
		W†	P	W/P	N
Statham, P23Db, TA1009	544 (15.8)				
TA1009D		480 (12.7)	211 (14.1)	394 (11.2)	142 (11.6)
D-250		324 (9.0)	186 (10.9)	344 (7.0)	125 (9.9)
Statham, P23Ia, TA1009	294 (7.2)				
TA1009D		319 (10.2)	324 (6.1)*	286 (9.2)	181 (7.0)*
D-250		396 (13.2)	56.5 (4.0)	423 (14.3)	54.1 (4.1)
Statham, P23ID, TA1010	302 (5.0)				
TA1010D		281 (7.1)	194 (9.2)	368 (6.9)	137 (10.3)
Bell & Howell, 4-327I, P/N368444	272 (22)				
P/N368787-0100		155 (10.5)	153 (11.7)	169 (11.7)	67.4 (8.2)
Bentley-Trantec, 800, D-210	400 (5.8)				
D-240		414 (10.9)	282 (10.6)	343 (10.8)	159 (13.9)

†See footnotes to table 2 for explanation of abbreviations

TABLE 5
Bandwidth of Transducers Fitted with Nondiaphragm Domes and Diaphragm Domes Applied with Each of 4 Technics

Transducer and dome tested	Bandwidth, Hz				
	Nondiaphragm dome	Diaphragm dome			
		Application technic			
		W†	P	W/P	N
Statham, P23Db, TA1009	119				
TA1009D		105	46.1	86.4	31.2
D-250		71.0	40.7	75.9	27.5
Statham, P23Ia, TA1009	64.9				
TA1009D		70.0	71.7*	62.7	39.9*
D-250		86.6	12.8	92.5	12.2
Statham, P23ID, TA1010	67.2				
TA1010D		61.9	42.5	81.1	30.0
Bell & Howell, 4-327I, P/N368444	59.4				
P/N368787-0100		34.0	33.5	37.1	14.8
Bentley-Trantec, 800, D-210	88.6				
D-240		90.8	61.8	75.3	34.7

†See footnotes to table 2 for explanation of abbreviations

TABLE 6
Rupture Pressure of Unsupported Diaphragm in Diaphragm Transducer Domes

Dome tested	Rupture pressure, torr				
	Dome 1	Dome 2	Dome 3	Dome 4	Dome 5
Statham, TA1009D	>5000	>5000	5000	>5000	4700
Bentley, D-250	>5000	5000	>5000	>5000	4200
Statham, TA1010D	3500	3200	3800	4000	4000
Bell & Howell, P/N368787-0100	150	150	500	150	600
Bentley, D-240	150	4500	>5000	>5000	>5000
Bell & Howell, P/N368787-0100*	600	600	500	550	550

*New domes not used in sensitivity or frequency-response test

of static inaccuracy, it should be held to a minimum. In our opinion, this minimum should not exceed 1 percent.

It is important to note that static inaccuracy, introduced by the improper application of a diaphragm dome, can only be detected by calibrating the transducer with known pressures following the application of the dome.

Transducer frequency response was also influenced by the type of dome used and the method of application. In each of the transducers tested, the frequency response with the nondiaphragm domes and with 25 of the 28 diaphragm-dome applications was acceptable, ie, the bandwidth exceeded 20 Hz. As was true for sensitivity and static accuracy, transducer frequency response is only 1 component of the dynamic accuracy of the total measurement system. However, unlike static accuracy, which can be determined by the summation of accuracy of the several system components, dynamic accuracy can only be determined by measuring accuracy, ie, bandwidth, of the composite system. In most clinical situations the pressure transducer is connected to an intra-arterial cannula by fluid-filled tubing. The tubing material, diameter, and length all affect the composite system bandwidth.[5] If the tubing is less rigid, of larger diameter, or longer, the system bandwidth will be less. Conversely, if the tubing is stiffer, of smaller diameter, or shorter, the system bandwidth will be greater. Generally, it is the fluid-filled tubing which limits the system bandwidth most severely. The smaller the bandwidth of the transducer-dome combination, the more important the characteristics of the tubing. Thus, selection of a transducer-dome combination with a large bandwidth is helpful in obtaining acceptable system dynamic accuracy.

The results of the diaphragm rupture tests indicate that maintenance of the integrity of this bacteriological shield should be anticipated with the pressure ranges normally encountered in the clinical setting. While pressurization of the unsupported dome is not recommended, the test data indicate that diaphragm rupture would be unlikely should this occur inadvertently.

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Amitriptyline Therapy Increases Electrocardiographic Changes During Reversal of Neuromuscular Blockade

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Induction of anesthesia is associated with an increased incidence of cardiac arrhythmias in patients maintained on amitriptyline medication. This study presents additional evidence showing that, in experimental animals (cats), amitriptyline treatment also produces significant ST-T wave and conduction abnormalities during neostigmine reversal of neuromuscular blockade.

Key Words—ATARACTICS, Tricyclic antidepressants. HEART, arrhythmias. ANTAGONISTS, neuromuscular relaxants.

THE tricyclic antidepressant amitriptyline has been shown to have cardiotoxic effects, particularly in patients with pre-existing heart disease,[1-4] including T-wave abnormalities, ventricular extrasystoles, tachycardia, and bundle-branch blocks.[2,5] In a study of 30 patients, Muller and Burckhardt demonstrated nonspecific flattening of T waves, decreased myocardial contractility and, in 2 patients, 1st degree heart block following 3 weeks of tricyclic antidepressant medication.[5] In another study, patients taking tricyclic antidepressant medication were shown to have increased susceptibility to cardiac arrhythmias in stressful situations, including induction of anesthesia.[2]

Based on this information, a study was undertaken to determine ECG changes during reversal of neuromuscular blockade in anesthetized cats treated for 28 days with amitriptyline. In some of the animals ECG was recorded during blockade reversal where the amitriptyline was discontinued 24 or 48 hours in advance; in others amitriptyline was continued until the time of the study.

METHODS

A total of 38 adult male cats were used in the study. Thirty cats received amitriptyline 1.5 mg/kg IM twice a day for 28 days. Eight cats were treated with physiological saline IM twice a day for 28 days.

28-Day Amitriptyline Treatment—Standard ECG leads, L1-L3, AVR, AVL, AVF, and V1-V6, were monitored weekly in each cat. Cats treated with physiological saline had normal ECG recordings throughout the treatment period. Cats treated with amitriptyline had ECG changes which usually appeared in the 2nd or 3rd week of treatment.

Reversal Experiments — After 28 days, reversal experiments were performed on the 8 cats treated with saline and 20 of the cats treated with amitriptyline. An additional 5 amitriptyline-treated cats were studied 24 hours after the last dose of amitriptyline, and 5 cats 48 hours after amitriptyline. All animals were anesthetized with chloralose (60 mg/kg, ip). A tracheostomy was performed and artificial ventilation maintained

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throughout the experiment. Blood pressure was monitored via a carotid artery cannula. The external jugular was cannulated for IV injections.

The right gastrocnemius muscle and sciatic nerve were isolated and connected to a twitch monitor and nerve stimulator as described elsewhere.[6] Standard ECG needle electrodes were placed to record L1-L3, AVR, AVL, AVF, and V1-V6 leads. Lead 2 was used when comparing the ECG recording of the various reversal drug groups.

A 1-hour stabilization period followed the above procedures. d-Tubocurarine (0.50 mg/kg) was then injected, producing complete neuromuscular blockade. After 25 percent recovery had occurred spontaneously, the remaining block was reversed, using neostigmine alone (6 cats), atropine and neostigmine simultaneously (6 cats), atropine followed in 5 minutes by neostigmine (6 cats), or physiological saline—no reversal (2 cats). The dose of atropine was 0.02 mg/kg, that of neostigmine 0.05 mg/kg. Body temperature (rectal) was monitored throughout the experiment and maintained at 36 to 37° C. Arterial blood gases and electrolytes were measured prior to and following reversal and found to be normal.

RESULTS

Electrocardiographic tracings shown in fig 1 and 2 demonstrate the typical ECG changes during amitriptyline treatment. Comparison of ECG recordings from weeks 1, 2, and 3 shows nonspecific ST-T wave changes occurring in cat 3 during week 3 (fig 1). In cat 5, 2 weeks of amitriptyline treatment caused a flattening of the ST segment, and after 3 weeks of amitriptyline, T-wave inversions were noted (fig 1). Cats 24 and 27 showed significant T-wave elevation in the 4th week of amitriptyline treatment (fig 2). Interestingly, 24 hours after amitriptyline, amitriptyline-induced T-wave elevations were still prominent, whereas 48 hours after amitriptyline there was a marked reduction in height.

Reversal Experiments — Reversal of curare blockade with neostigmine alone or with atropine-neostigmine had no effect on the ECGs of cats chronically treated with physiological saline.

GROUP A. Neostigmine Alone: Amitriptyline Treated (Fig 3)—Reversal of d-tubocurarine block using neostigmine alone resulted in an intensification of the pre-existing ECG abnormalities primarily involving the ST segment in all 6 animals given amitriptyline up to the time of the study. In 1 cat an intraventricular conduction defect was also noted upon reversal.

GROUP B. Atropine-Neostigmine Mixed: Amitriptyline Treated (Fig 4)—d-Tubocurarine reversal with an atropine-neostigmine mixture also intensified pre-existing ECG changes in all of the 6 cats given amitriptyline for 28 days. In 1 cat prominent changes in ST-T wave were seen and 1 cat developed an intraventricular conduction defect. The remaining cats in this group demonstrated varying degrees of ST-T wave changes.

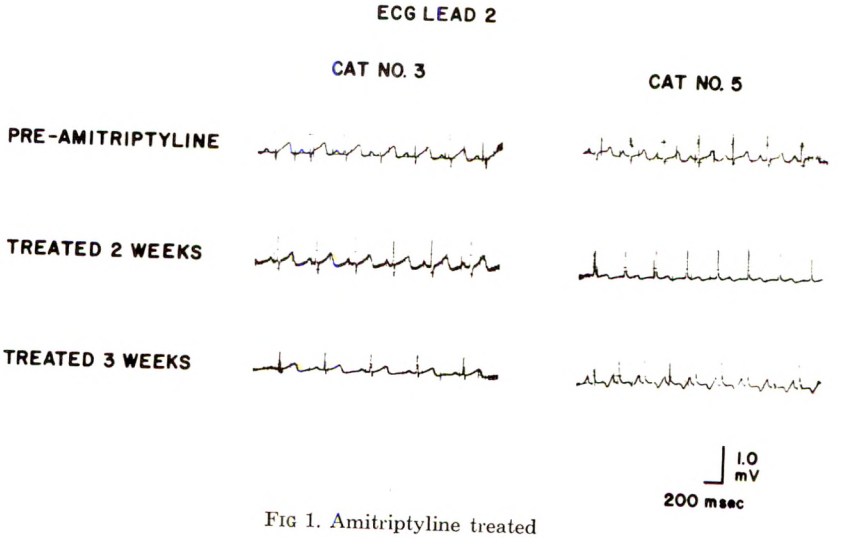


FIG 1. Amitriptyline treated

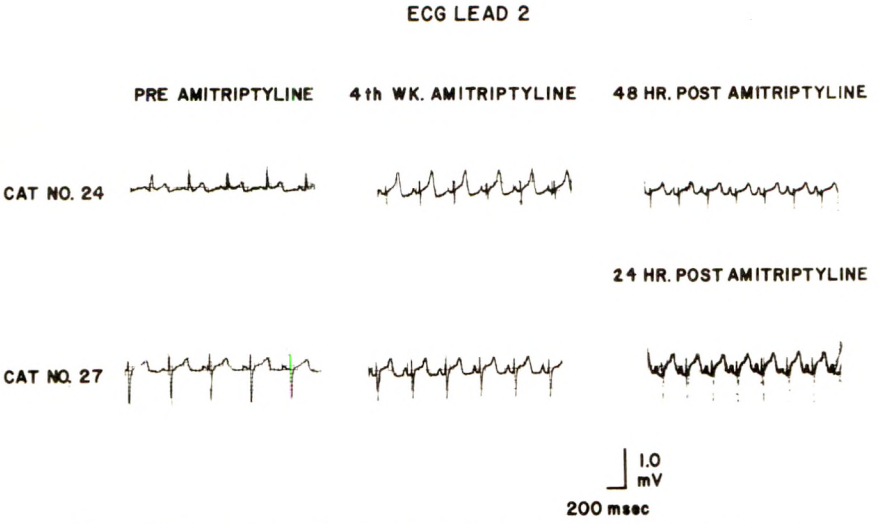


FIG 2. Electrocardiographic changes with chronic amitriptyline treatment

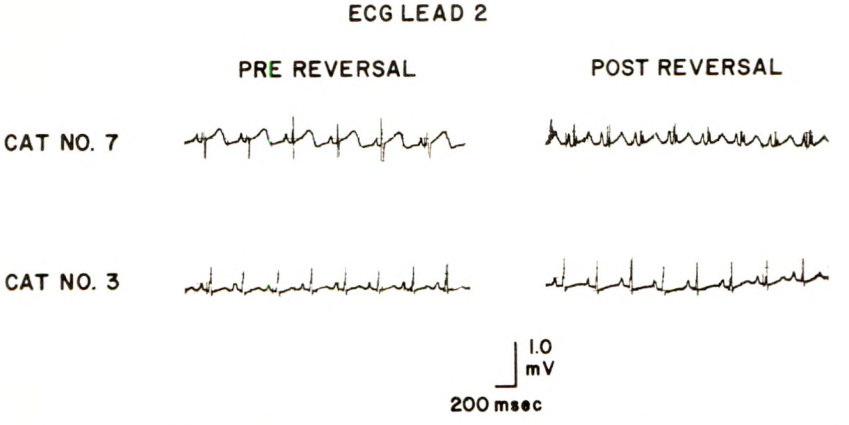


FIG 3. 28 day amitriptyline treated d-tubocurarine reversal with neostigmine alone

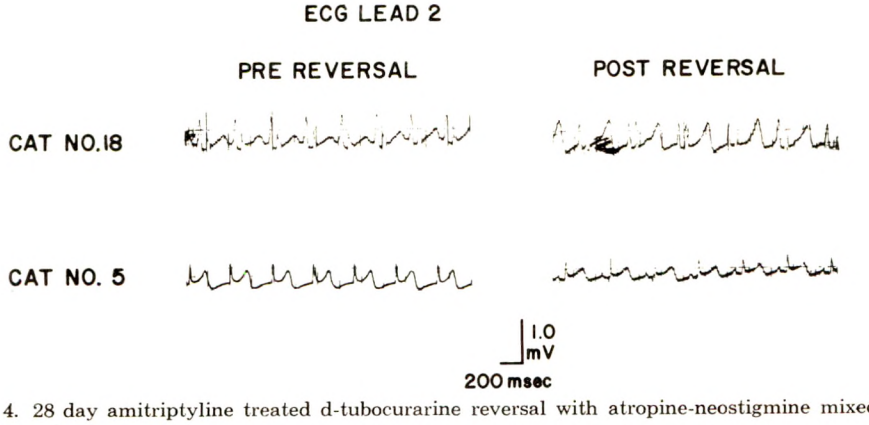


FIG 4. 28 day amitriptyline treated d-tubocurarine reversal with atropine-neostigmine mixed

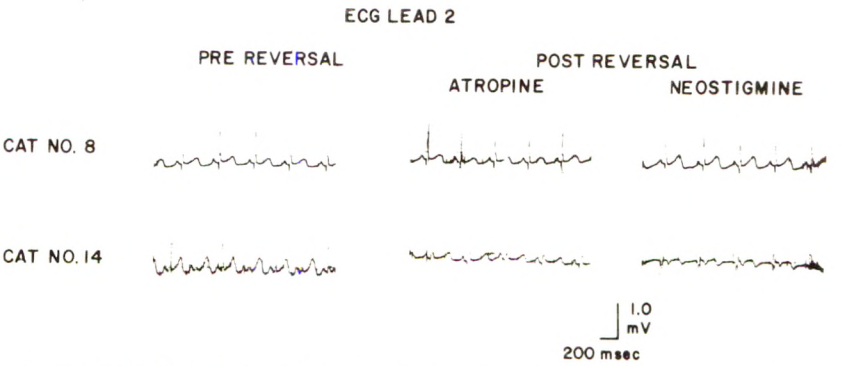


FIG 5. 28 day amitriptyline treated d-tubocurarine reversal with atropine—5-min-neostigmine

GROUP C. Atropine-5 Minutes-Neostigmine: Amitriptyline Treated (Fig 5) — In this group of 6 cats, reversal of the d-tubocurarine block with atropine, followed after 5 minutes by neostigmine, was unassociated with ECG changes following the atropine alone, but when neostigmine was administered pre-existing ST-T wave abnormalities became intensified in all of the cats.

GROUP D. No Reversal (Saline Injection): Amitriptyline Treated (Not Shown) —Two cats received an injection of physiological saline in place of the reversing drug to determine if the injection itself had any effect upon the ECG. ECGs before and after injection were the same.

Post Amitriptyline — Forty-eight hours after the last dose of amitriptyline, reversal of d-tubocurarine with neostigmine alone (3 cats) or a mixture of atropine and neostigmine (2 cats) had no effect on the ECG of any animal. In these animals the ECG showed no amitriptyline effect prior to reversal. When d-tubocurarine blockade was reversed with neostigmine (3 cats) or atropine-neostigmine mixed (2 cats) 24 hours after the last dose of amitriptyline, the ECG did not change even though in some animals amitriptyline-induced ECG changes were still present.

DISCUSSION

Our study demonstrates cardiac changes involving ST-T wave and myocardial conduction in cats during chronic amitriptyline treatment. In the presence of amitriptyline-induced ECG changes, neostigmine reversal of neuromuscular blockade during anesthesia caused pronounced increases in the severity of these abnormalities. If, however, the amitriptyline medication were discontinued at least 24 hours prior to reversal, the ECG was not influenced by the reversal.

The progressive ECG changes seen in our study with chronic therapeutic doses of amitriptyline are identical to ECG changes reported in patients chronically maintained on tricyclic medication.[5,7,8]

Most common of the reported changes are nonspecific ST-T wave changes. Least common are prolonged P-R and QRS intervals and A-V conduction disturbances. Muller and Burckhardt reported that 2 out of 30 patients treated with a variety of tricyclic antidepressants developed 1st-degree heart block.[5] These investigators also found decreased myocardial contractility in a significant number of patients treated with tricyclic antidepressants.

A question as to whether ECG changes seen in patients without a history of cardiac disease at relatively low tricyclic dosage might lead to more prominent conduction disturbances or arrhythmias during stressful situations has been raised by several investigators.[2,8]

We in the present investigation found that reversal of d-tubocurarine blockade with neostigmine alone or with atropine and neostigmine causes a marked intensification in amitriptyline-induced ECG abnormalities, which in our study consisted primarily of nonspecific ST-T wave changes and occasional conduction disturbances. Anesthesia itself is a stressful event, and each of the components of anesthesia, eg, induction, intubation, reversal of muscle blockade, and reversal of anesthesia, may contribute to the overall stress of anesthesia.

Our findings support the hypothesis that stress on a heart with tricyclic-induced ECG abnormalities can increase the prominence of these abnormalities.

In a related study, Moir et al published

findings concerned with sudden unexpected deaths during amitriptyline therapy.[2] The occurrence of cardiac arrhythmias was recorded in patients during a stress situation, in this case thiopental induction preceding electroconvulsive therapy. One-third of the patients were taking tricyclic antidepressant medication, of whom 11 percent were taking amitriptyline. The authors found that patients taking the tricyclic medication had arrhythmias 31 percent more often than did other patients. Although the authors could not prove statistical significance in their data, they emphasized that none of the patients had pre-existing cardiac disease.

Both age and pre-existing heart disease are reported to increase the cardiac complications associated with tricyclic therapy.[2,8] It seems reasonable to assume that both age and heart disease could adversely contribute to the cardiac effects reported in this study.

The exact mechanism by which tricyclic antidepressant drugs produce their cardiotoxic effects is poorly understood. We also cannot explain the mechanism of intensification of amitriptyline-induced ECG changes observed during neostigmine reversal of neuromuscular blockade. Kantor et al[7] demonstrated that the cardiotoxic effects of therapeutic doses of tricyclic drugs are directly related to plasma levels of the tricyclic drug and its active metabolites.

Newton[9] suggested that the cardiac effects of tricyclic drugs were due to a direct action of the drug itself or its metabolites on the myocardium. Bigger et al[10] recently concluded that the cardiotoxic effects of imipramine are due to a quinidine-like activity on the heart.

In our experiments the ECG abnormalities were not intensified during neostigmine reversal of the muscle blockade 24 to 48 hours after the last dose of amitriptyline. Spiker and Biggs[11] reported the half-lives of amitriptyline and nortriptyline, its active metabolite, to be 17 and 18 to 32 hours, respectively. Kantor et al[7] reported that an imipramine-induced A-V heart block disappeared 23 hours after the last administration of the drug; the half-life of imipramine is 20 to 30 hours.

The fact that neostigmine reversal had no effect on the ECG beyond the half-life for amitriptyline and its active metabolite suggests that therapeutic plasma and tissue levels of amitriptyline are necessary for the observed neostigmine reversal effects on the ECG.

ACKNOWLEDGMENT

The authors gratefully acknowledge the assistance of Cathy Zurales and Dr. K. B. Ramakrishnaiah.

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Guest Discussion

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Since the early reports of cardiac arrest and dysrhythmias following neostigmine administration,[1-3] various technics have been suggested to enhance the safety of reversal. These technics include respiratory alkalosis,[4] maintenance of oxygenation,[5] atropine followed by neostigmine,[6] atropine-neostigmine mixture,[7-9] slow administration of the mixture,[6,10] titration of the exact dose by a nerve stimulator,[6] substituting glycopyrrolate for atropine,[11,12] and substituting pyridostigmine for neostigmine.[13] From these technics, simultaneous injection of

TABLE
Suggested Contraindications to Antagonism with Neostigmine

Cardiac effects
Acidemia and hypercarbia (Riding and Robinson, 1961)[4]
Hypoxemia (Baraka, 1968)[5]
Severe heart disease (Owens et al, 1976)[14]
Pre-existing dysrhythmias and heart block
"Fully" digitalized patients (Ivankovic et al, 1971)[15]
Geriatric patients (Owens et al, 1976)[14]
Patients on tricyclic antidepressants (Glisson et al, 1978)
Respiratory effects
Asthma
Intestinal effects
Bowel anastomosis (Bell and Lewis, 1968)[16]

atropine and neostigmine while ensuring adequate oxygenation has been widely accepted.

In a report published in 1970,[9] it was clinical experience, antagonism of antidepolarizing block with atropine-neostigmine mixture appears to be safe in the vast majority of our patients. What remains undefined is when and why it may be dangerous in certain instances. In the literature, certain conditions have been suggested as possible contraindications to the use of neostigmine for reversal (table).

In a report published in 1970,[9] it was found that atropine-neostigmine mixture did not cause any serious hazards or dangerous dysrhythmias in pediatric patients with congenital cardiac disease. Changes in heart rate were similar to the changes reported earlier by Baraka in adult patients.[8] In the majority of these patients, sinus rhythm was maintained during and after reversal.[9] A few patients developed an abnormal rhythm temporarily, while interestingly enough, some patients with an abnormal rhythm converted to normal sinus rhythm following the injection of the mixture.[9] More recently, examination of the immediate hemodynamic responses to the injection of the mixture in healthy children revealed that the initial rise and delayed fall in heart rate were associated with opposite changes in stroke volume index.[17] Consequently, cardiac output remained essentially unchanged throughout the period of observation.[17]

This interesting study by Dr. Glisson and his associates suggests that neostigmine administration in cats chronically treated with amitryptyline intensifies the already existing ST and T wave changes and on occasion may result in conduction defects. Their work further suggests that atropine pretreatment does not prevent their occurrence, while if amitryptyline is discontinued for 24 hours or longer, neostigmine does not result in any ECG changes. Such a recommendation may contribute to the safety of neostigmine administration in patients on amitryptyline therapy.

Dr. Glisson and his group are to be commended for such an important piece of work. However, before final conclusions can be made, the following questions need to be answered: (1) Were the ECG changes really hazardous? (2) Would increasing the dose of atropine prevent some of these dysrhythmias? (3) With frequent reports documenting the unwanted cardiac effects of amitryptyline[18] through multitudes of action, is it not time to think about abandoning the drug?

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The effect of heparin solution in syringes on the determination of arterial blood P_{CO_2}, pH, and bicarbonate was examined. Dilution of blood by heparin solution did not significantly affect the pH of blood samples but reduced the measured P_{CO_2} and the calculated bicarbonate and base excess in direct proportion to the amount of dilution. When used in normal quantities as an anticoagulant, lubricant, and filler of needle and syringe dead space, heparin solution caused a 17 percent or greater reduction in P_{CO_2} and bicarbonate in approximately 20 percent of the arterial blood samples received for analysis. Such unrecognized error could cause misinterpretation of acid-base status. Increasing the sample volume and decreasing the amount of heparin used will reduce the error. *(Hansen JE, Simmons DH: A systematic error in the determination of blood P_{CO_2}. Am Rev Respir Dis 115:1061-1063, 1977)*

Cardiovascular Responses to Nitrous Oxide During Light, Moderate, and Deep Halothane Anesthesia in Man

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The cardiovascular effects of addition of 20, 40, and then 60 percent N_2O or nitrogen during controlled ventilation with light (0.8 percent), moderate (1.2 percent), and deep (1.6 percent) halothane-O_2 anesthesia were determined in 39 volunteers and compared to results obtained in 18 additional volunteers who received similar concentrations of halothane-O_2 anesthesia alone over the same time interval.

Halothane resulted in significant and similar reductions in heart rate at all concentrations studied but produced concentration-related decreases in mean arterial blood pressure, stroke volume, and cardiac output and increases in right atrial pressure. Halothane did not significantly change peripheral resistance at any concentration. Addition of N_2O did not change arterial blood pressure or heart rate at any concentration of halothane but produced increases in right atrial pressure in all groups. Peripheral resistance was reduced and stroke volume and cardiac output increased when N_2O was added to 0.8 percent halothane. Subjects anesthetized with 1.2 percent halothane showed no significant change in stroke volume or cardiac output with addition of any concentration of N_2O, while those anesthetized with 1.6 per cent halothane sustained reductions in stroke volume and cardiac output with 60 percent N_2O. Peripheral resistance remained unaltered during addition of N_2O to 1.2 percent halothane but significantly increased with 1.6 percent halothane. Addition of nitrogen to halothane produced changes that were similar to those occurring during continued halothane-O_2 administration. These data demonstrate that addition of N_2O during halothane-O_2 anesthesia produces significant changes in cardiovascular dynamics which are variable and dependent upon the concentrations of halothane and N_2O employed. Our findings suggest that N_2O blocks the reduction of peripheral vascular resistance and increases in cardiac output, stroke volume, and heart rate seen with continued halothane-O_2 administration when added to moderate or deep levels of halothane.

Key Words—ANESTHETICS, gases, nitrous oxide. ANESTHETICS, volatile, halothane. HEART, function, nitrous oxide.

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Use of N_2O as a supplement during halothane anesthesia has produced evidence of cardiovascular stimulation as well as depression.[1,2] The effects of increasing concentrations of N_2O on cardiovascular dynamics has not been measured during halothane anesthesia. In the present study, dose-response effects of N_2O on cardiovascular dynamics during light (1.0 MAC), moderate (1.5 MAC), and deep (2.0 MAC) halothane-O_2 anesthesia were determined in healthy adult volunteers and compared to the effects of adding similar concentrations of nitrogen or maintaining a constant concentration of halothane and O_2 over the same time period.

METHODS

The study was approved by the University of Utah Human Experimental Committee. Written informed consent was obtained from a total of 57 adult male volunteers, aged 21 to 28 years, who served as the experimental subjects. Each volunteer arrived in the operating room between 0800 and 1100 hours after an overnight fast. An IV infusion was started in an arm vein, a catheter was placed in a radial artery and threaded into the central aorta, and a central venous catheter was placed into an antecubital vein and threaded into the right atrium. The central aortic catheter was attached to a computer substation in the operating room and, after appropriate calibration as previously described,[3] computer analysis of the central aortic pulse pressure wave was used to determine cardiac output, stroke volume, heart rate, mean aortic blood pressure, and peripheral vascular resistance during control conditions (breathing room air). Following collection of control data, 19 volunteers (group 1) were given 1.0 to 1.2 percent halothane in O_2 through a standard anesthesia face mask. Respirations were first assisted and then controlled to maintain arterial CO_2 tension ($Paco_2$) as measured in arterial blood every 15 to 20 minutes, between 30 and 35 torr. A semi-closed-circle system provided CO_2 absorption and a total fresh gas inflow of 5 to 6 L/min. Endotracheal intubation was performed without the use of a muscle relaxant after a minimum of 40 minutes (range 40 to 51 minutes) of anesthesia. Following intubation a constant end-expired halothane concentration of 0.8 percent (approximately 1 MAC) in O_2 was maintained for 30 minutes (via frequent end-tidal sampling, analysis with a Beckman infrared analyzer, and flowmeter adjustment). Twenty percent N_2O was then added to the inspired mixture of gases of 9 of the volunteers and cardiovascular data recorded 20 minutes later. Following this, the concentration of N_2O was changed to 40 percent for 20 minutes and cardiovascular dynamics again recorded. Data were obtained in a similar fashion (1) after 20 minutes of breathing 60 percent N_2O; (2) 20 minutes after turning off N_2O (but continuing the same end-expired concentration of halothane in O_2); and (3) one and (4) two hours after endotracheal tube extubation and termination of all anesthesia. During addition and removal of N_2O from the inspired gases, end-tidal halothane concentration was frequently measured and kept constant. Four of the remaining volunteers in group 1 were treated in a similar fashion to those given N_2O, except that nitrogen was substituted for N_2O. The remaining 6 volunteers in group 1 received halothane-O_2 only. In these volunteers, cardiovascular variables were recorded at the same time intervals as for those who received N_2O or nitrogen. The above studies were repeated in a similar fashion in 38 additional volunteers, 19 anesthetized with a constant end-tidal concentration of 1.2 percent halothane (1.5 MAC—group 2) and 19 with 1.6 percent halothane (2.0 MAC—group 3).

Data were analyzed for statistical significance using Student's paired and unpaired t-tests; p values of <0.05 were regarded as significant.

RESULTS

$Paco_2$ and arterial pH were similar in the 3 groups of volunteers during control conditions and did not significantly change during any of the subsequent study periods. Dilution of inspired gases with either nitrogen or N_2O resulted in similar concentration-related decreases in arterial O_2 tension (Pao_2). No subject had a Pao_2 below 90 torr at any time.

Halothane produced concentration-related decreases in mean arterial blood pressure, stroke volume, and cardiac output and increases in mean right atrial pressure (tables 1 to 4). Halothane resulted in significant but similar reductions in heart rate at all concentrations studied (table 5) but did not significantly alter peripheral arterial resistance at any concentration (table 6).

Addition of N_2O did not change arterial blood pressure or heart rate at any concentration of halothane but 60 percent N_2O increased right atrial pressure in all groups.

TABLE 1

Mean Arterial Blood Pressure (Torr) Before, During, and After Administration of Halothane-O_2, Halothane-N_2O-O_2, and Halothane-Nitrogen-O_2 (Mean ± SD)

End-tidal halothane concentration	0.8%			1.2%			1.6%		
Unanesthetized MAP	91 ± 11			95 ± 14			94 ± 10		
MAP during halothane + O_2	73 ± 8*			68 ± 10†			63 ± 6‡		
	N_2O	N_2	O_2	N_2O	N_2	O_2	N_2O	N_2	O_2
20% N_2O or N_2 or 50 min of halothane + O_2	75* ±10	70* ±7	73* ±9	71† ±7	66† ±15	67† ±12	64‡ ±9	66‡ ±9	55‡ ±6
40% N_2O or N_2 or 70 min of halothane + O_2	77* ±11	74* ±6	72* ±9	70† ±10	68† ±12	68† ±10	65† ±8	70† ±7	63‡ ±5
60% N_2O or N_2 or 90 min of halothane + O_2	77* ±9	76* ±6	72* ±6	70† ±8	71* ±7	73* ±12	69† ±7	66† ±4	67† ±7
0% N_2O or N_2 or 110 min of halothane + O_2	79* ±12	76* ±7	87‖ ±7	74* ±7	72* ±9	78*‖ ±9	69† ±6	71†‖ ±7	70†‖ ±8
1 Hr postanesthesia	91‖ ±8	88‖ ±12	101¶ ±12	90‖ ±9	92‖ ±6	100¶ ±12	88‖ ±7	96** ±10	85¶ ±7
2	93‖ ±12	92‖ ±6	100¶ ±13	93‖ ±8	92‖ ±8	97¶ ±9	91‖ ±4	95** ±8	88¶ ±8

*$p<0.05$, †$p<0.025$, ‡$p<0.01$, §$p<0.005$; Student's paired t-test when compared to unanesthetized data

‖$p<0.05$, ¶$p<0.025$, **$p<0.01$; Student's paired t-test when compared to halothane + O_2 data

TABLE 2

Stroke Volume (ML) Before, During and After Administration of Halothane-O_2, Halothane-N_2O-O_2, and Halothane-Nitrogen-O_2, (Mean ± SD)

End-tidal halothane concentration	0.8%			1.2%			1.6%		
Unanesthetized SV	57 ± 6			54 ± 6			56 ± 6		
SV during halothane + O_2	44 ± 9*			37 ± 5†			33 ± 8‡		
	N_2O	N_2	O_2	N_2O	N_2	O_2	N_2O	N_2	O_2
20% N_2O or N_2 or 50 min of halothane + O_2	45* ±7	46* ±8	44* ±5	35† ±7	34† ±7	36† ±6	31‡ ±7	32‡ ±6	33‡ ±6
40% N_2O or N_2 or 70 min of halothane + O_2	47* ±6	48* ±7	47* ±6	37† ±7	36† ±6	39† ±7	28‡ ±7	33‡ ±6	35‡ ±5
60% N_2O or N_2 or 90 min of halothane + O_2	50‖ ±6	54‖ ±6	54‖ ±3	39† ±8	40† ±9	41† ±5	26‡‖ ±5	35† ±7	40†‖ ±3
0% N_2O or N_2 or 110 min of halothane + O_2	57‖ ±6	57‖ ±5	55‖ ±6	44*‖ ±6	43*‖ ±7	45*‖ ±5	33‡ ±6	35† ±5	40†‖ ±6
1 Hr postanesthesia	58‖ ±12	61‖ ±5	55‖ ±8	55¶ ±7	47‖ ±6	51¶ ±8	54‖ ±4	52‖ ±10	53¶ ±8
2	60‖ ±7	60‖ ±8	58‖ ±6	53¶ ±7	46‖ ±7	53¶ ±6	57‖ ±4	56¶ ±9	55¶ ±6

*$p<0.05$, †$p<0.025$, ‡$p<0.01$, §$p<0.005$; Student's paired t-test when compared to unanesthetized data

‖$p<0.05$, ¶$p<0.025$, **$p<0.01$; Student's paired t-test when compared to halothane + O_2 data

TABLE 3
Cardiac Output (L/Min) Before, During and After Administration of Halothane-O_2, Halothane-N_2O-O_2, and Halothane-Nitrogen-O_2 (Mean ± SD)

End-tidal halothane concentration	0.8%			1.2%			1.6%		
Unanesthetized CO	4.2 ± 0.5			4.3 ± 0.5			4.3 ± 0.4		
CO during halothane + O_2	3.4 ± 0.6*			2.8 ± 0.4†			2.4 ± 0.3‡		
	N_2O	N_2	O_2	N_2O	N_2	O_2	N_2O	N_2	O_2
20% N_2O or N_2 or 50 min of halothane + O_2	3.5* ±0.5	3.5* ±0.6	3.8* ±0.4	2.7† ±0.7	2.8* ±0.4	2.9† ±0.4	2.1‡ ±0.4	2.3‡ ±0.3	2.5‡ ±0.4
40% N_2O or N_2 or 70 min of halothane + O_2	3.7 ±0.5	3.6* ±0.4	3.8* ±0.4	2.9† ±0.6	3.1* ±0.5	3.1† ±0.5	2.0‡ ±0.5	2.5‡ ±0.4	2.9‡ ±6.6
60% N_2O or N_2 or 90 min of halothane + O_2	4.0*‖ ±0.6	4.2¶ ±0.4	4.2‖ ±0.4	3.0† ±0.4	3.9‖ ±0.6	3.9*‖ ±0.6	1.9‡‖ ±0.3	3.1*‖ ±0.3	3.4*‖ ±0.3
0% N_2O or N_2 or 110 min of halothane + O_2	4.2*‖ ±0.5	4.4¶ ±0.5	4.7¶ ±0.3	3.30†‖ ±0.5	3.9† ±0.3	4.1¶ ±0.4	2.2‡ ±0.4	3.3*‖ ±0.4	3.6‖ ±0.5
1 Hr postanesthesia	4.1‖ ±0.3	4.4¶ ±0.5	4.7** ±0.3	4.0¶ ±0.6	3.9‖ ±0.6	4.5¶ ±0.4	3.6‖ ±0.5	4.1¶ ±0.4	4.9** ±0.4
2	4.4‖ ±0.4	4.2‖ ±0.4	4.1‖ ±0.5	4.4¶ ±0.5	4.2‖ ±0.5	4.9** ±0.6	3.9** ±0.4	4.2¶ ±0.4	4.6¶ ±0.3

*$p<0.05$, †$p<0.025$, ‡$p<0.01$, §$p<0.005$; Student's paired t-test when compared to unanesthetized data

‖$p<0.05$, ¶$p<0.025$, **$p<0.01$; Student's paired t-test when compared to halothane + O_2 data

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TABLE 4

Right Atrial Pressure (Torr) Before, During, and After Administration of Halothane-O_2, Halothane-N_2O-O_2, and Halothane-Nitrogen-O_2 (Mean ± SD)

End-tidal halothane concentration	0.8%			1.2%			1.6%		
Unanesthetized RAP	4.4 ± 1.8			4.3 ± 2.2			4.5 ± 1.7		
RAP during halothane + O_2	6.3 ± 1.7*			6.9 ± 1.7†			8.4 ± 1.0‡		
	N_2O	N_2	O_2	N_2O	N_2	O_2	N_2O	N_2	O_2
20% N_2O or N_2 or 50 min of halothane + O_2	6.7* ±2.4	5.8 ±0.9	5.2 ±1.2	7.9† ±1.1	7.6† ±2.0	7.7† ±0.9	8.9† ±1.3	8.5‡ ±1.4	8.1‡ ±1.2
40% N_2O or N_2 or 70 min of halothane + O_2	7.8* ±1.9	6.1 ±1.2	5.0 ±1.5	8.8‡ ±1.0	6.2 ±1.9	6.0 ±0.9	9.6† ±1.2	8.0† ±0.9	7.0† ±1.3
60% N_2O or N_2 or 90 min of halothane + O_2	8.7†‖ ±2.1	6.0 ±1.2	5.4 ±1.1	9.6‡‖ ±1.2	6.2 ±1.6	6.4 ±1.1	12.0§¶ ±1.3	8.0† ±0.5	7.0† ±1.1
0% N_2O or N_2 or 110 min of halothane + O_2	7.1* ±2.9	5.7 ±1.6	5.0 ±0.9	8.7‡‖ ±0.9	6.6 ±1.4	6.0 ±1.4	10.1§‖ ±1.1	8.3 ±1.2	6.5‖ ±1.4
1 Hr postanesthesia	6.0 ±1.6	4.8 ±2.1	4.4 ±1.1	6.0 ±1.8	4.9 ±2.4	5.2 ±0.8	6.0 ±1.3	6.6 ±1.3	4.5¶ ±1.2
2	4.6 ±2.1	4.8 ±1.6	4.3 ±1.6	6.0 ±0.9	5.2 ±1.1	4.9 ±1.2	5.9 ±1.4	6.0 ±1.1	5.1¶ ±1.1

*$p<0.05$, †$p<0.025$, ‡$p<0.01$, §$p<0.005$; Student's paired t-test when compared to unanesthetized data

‖$p<0.05$, ¶$p<0.025$, **$p<0.01$; Student's paired t-test when compared to halothane + O_2

TABLE 5
Heart Rate (Beats/Min) Before, During and After Administration of Halothane-O_2, Halothane-N_2O-O_2, and Halothane-Nitrogen-O_2 (Mean ± SD)

End-tidal halothane concentration	0.8%			1.2%			1.6%		
Unanesthetized HR	77 ± 10			77 ± 8			73 ± 7		
HR during halothane + O_2	69 ± 5*			67 ± 6*			65 ± 6*		
	N_2O	N_2	O_2	N_2O	N_2	O_2	N_2O	N_2	O_2
20% N_2O or N_2 or 50 min of halothane + O_2	68* ±6	67* ±8	72* ±6	68* ±7	66* ±5	71* ±5	68* ±6	62* ±6	63† ±3
40% N_2O or N_2 or 70 min of halothane + O_2	68* ±5	70* ±6	73* ±6	67* ±6	71‡ ±5	71* ±6	68* ±5	66* ±8	67† ±4
60% N_2O or N_2 or 90 min of halothane + O_2	70* ±5	74 ±5	77‖ ±4	70* ±7	74‡ ±6	80‖ ±4	66* ±6	72‖ ±6	73‖ ±5
0% N_2O or N_2 or 110 min of halothane + O_2	75‖ ±4	70 ±8	79‖ ±6	70* ±5	78‖ ±7	83‖ ±6	70* ±7	75‖ ±8	77‖ ±4
1 Hr postanesthesia	77‖ ±12	76‖ ±5	77‖ ±5	73 ±7	70* ±5	82‖ ±8	72 ±6	76‖ ±5	76‖ ±6
2	75‖ ±10	81‖ ±6	75‖ ±5	76 ±6	70‖ ±9	82‖ ±7	72 ±8	77‖ ±10	76‖ ±7

*$p<0.05$, †$p<0.025$, ‡$p<0.01$, §$p<0.005$; Student's paired t-test when compared to unanesthetized data

‖$p<0.05$, ¶$p<0.025$, **$p<0.01$; Student's paired t-test when compared to halothane + O_2

TABLE 6

Peripheral Vascular Resistance (PRU) Before, During, and After Halothane-O_2, Halothane-N_2O-O_2, and Halothane-Nitrogen-O_2 (Mean ± SD)

End-tidal halothane concentration	0.8%			1.2%			1.6%		
Unanesthetized PVR	214 ± 22			236 ± 18			219 ± 16		
PVR during halothane + O_2	219 ± 16			241 ± 23			227 ± 18		
	N_2O	N_2	O_2	N_2O	N_2	O_2	N_2O	N_2	O_2
20% N_2O or N_2 or 50 min of halothane + O_2	228 ±18	220 ±18	225 ±12	222 ±18	261 ±12	250 ±18	260*‖ ±19	210 ±12	228 ±21
40% N_2O or N_2 or 70 min of halothane + O_2	210 ±12	212 ±16	210 ±16	210 ±18	242 ±19	230 ±16	285†¶ ±12	202‖ ±16	215 ±12
60% N_2O or N_2 or 90 min of halothane + O_2	191*‖ ±23	174†¶ ±12	165†¶ ±12	208 ±21	222 ±12	220 ±21	308‡‖ ±11	201‖ ±12	205‖ ±13
0% N_2O or N_2 or 110 min of halothane + O_2	180†¶ ±19	164†¶ ±7	159†¶ ±16	218 ±12	218 ±16	202‖ ±19	255* ±12	193‖ ±8	195‖ ±16
1 Hr postanesthesia	200 ±17	221 ±12	232 ±16	212 ±16	261 ±12	238 ±16	226 ±12	226 ±15	235 ±21
2	198 ±12	231 ±16	231 ±21	219 ±14	256 ±19	242 ±21	216 ±18	233 ±19	241 ±16

*$p<0.05$, †$p<0.025$, ‡$p<0.01$, §$p<0.005$; Student's paired t-test when compared to unanesthetized data
‖$p<0.05$, ¶$p<0.025$, **$p<0.01$; Student's paired t-test when compared to halothane + O_2

Peripheral resistance decreased and stroke volume and cardiac output increased when N_2O was added to group 1 volunteers (those anesthetized with 0.8 percent halothane). These changes were first noticeable with 20 percent N_2O but only became statistically significant with 40 percent N_2O with regard to peripheral resistance, and with 60 percent N_2O with regard to stroke volume and cardiac output. Group 2 subjects showed no significant change in stroke volume or cardiac output upon addition of N_2O at any concentration of N_2O, while group 3 sustained reductions of both variables upon addition of 60 percent N_2O. Peripheral resistance remained unaltered during addition of N_2O in individuals anesthetized with 1.2 percent halothane (group 2) but significantly increased in those receiving 1.6 percent (group 3). Termination of N_2O generally produced small increases in arterial blood pressure, heart rate, stroke volume, and cardiac output and decreases in right atrial pressure.

Continued administration of halothane-O_2 anesthesia (instead of addition of N_2O) resulted in significant time-dependent increases in heart rate, stroke volume, cardiac output, and arterial blood pressure and decreases in peripheral arterial resistance at all concentrations of halothane. Addition of nitrogen (instead of N_2O) to halothane produced changes similar to those occurring during continued halothane-O_2 administration.

Termination of anesthesia resulted in a return of all variables to values not significantly different from preanesthesia controls within 2 hours.

DISCUSSION

The results of this study demonstrate that addition and removal of N_2O during halothane-O_2 anesthesia produce significant changes in cardiovascular dynamics, which are variable and dependent upon the concentrations of halothane and N_2O employed. After equilibration with 1.6 percent halothane in O_2, addition of N_2O resulted in an increase in peripheral arterial resistance and a tendency toward decreases in stroke volume and cardiac output. In contrast, adding N_2O during 1.2 percent halothane in O_2 changed only right atrial pressure, while adding the gas during 0.8 percent halothane in O_2 caused a significant reduction in peripheral arterial resistance and increases in stroke volume and cardiac output. Increases in stroke volume, heart rate, and cardiac output and decreases in peripheral arterial resistance upon addition of N_2O during 0.8 percent halothane in O_2 were significantly less* than those occurring during continued administration of the same concentration of halothane and O_2 over the same time interval. These findings suggest that N_2O blocks the reduction in peripheral vascular resistance and increases in cardiac output and stroke volume observed during prolonged, continued halothane-O_2 administration, especially when added during moderate or deep levels of halothane.

Changes similar to those observed with 60 percent N_2O in this study have been reported by Hornbein and coworkers[1] when 70 percent N_2O was added to the inspired mixture of gases of volunteers spontaneously breathing 1 and 2 MAC halothane in O_2. Hornbein et al suggested that the differences seen with the 2 concentrations of halothane in his study might be related to greater depression of respiration and a significantly higher arterial CO_2 tension at 2 MAC halothane. This could not explain the findings in our study since arterial CO_2 tension was maintained at a constant level.

While the mechanism(s) responsible for our findings as well as for those of Hornbein and coworkers is not entirely clear, it appears to be related to the cardiovascular stimulating effects of prolonged halothane exposure. A number of authors[4-6] have shown that cardiac function recovers during prolonged continuous administration of halothane. Recovery is time dependent, more noticeable during administration of higher concentrations of halothane, and similar to what would be observed if a beta-adrenergic stimulating drug was administered (increases in heart rate, stroke volume, and cardiac output and a decrease in peripheral arterial resistance). The basis for this apparent beta-adrenergic-like stimulation is unknown. The influence of N_2O and lowered concentrations of O_2 in modifying the cardiovascular stimulating effects of prolonged halothane administration was, at least until this study, also unknown. The time requirement of halothane-O_2 administration before 20 percent N_2O or nitrogen was added to the inspired gases (70 to 80 minutes) and, even more importantly, before measurements with 60 percent concentrations of the gases (130 to 145 minutes) were made in this study, is in the range which has been

*$p<0.05$; Student's unpaired t-test

shown to result in cardiovascular stimulation with continued halothane administration.[5] Since addition of nitrogen produced changes in dynamics in all groups similar to those that occurred with continuous halothane-O_2 administration, differences in cardiovascular dynamics between volunteers given N_2O and those receiving continuous halothane-O_2 cannot be attributed to a lowered inspired concentration of O_2. Furthermore, termination of N_2O caused all variables to return toward values that would have occurred if N_2O had not been administered.

All of the foregoing suggests that N_2O antagonizes the cardiovascular stimulating effects of prolonged halothane administration. Why this antagonism is incomplete at low concentrations of halothane and results in changes compatible with cardiovascular depression (decreased cardiac output and elevation of peripheral vascular resistance) at high concentrations of halothane is unknown at this time. Perhaps N_2O administration during high concentrations of halothane is associated with increased circulating levels of norepinephrine. On the other hand, it is possible these changes are much more complex and are related to an interaction of direct and indirect myocardial effects of the 2 anesthetics, norepinephrine release, and total depth of anesthesia. The cardiovascular effects of prolonged N_2O administration alone have not been carefully studied. Knowledge of these effects may help to explain our findings.

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Guest Discussion

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It has become increasingly apparent that N_2O is not simply an inert vehicle for the delivery of potent vapors. Nitrous oxide has effects of its own and, as the report by Hill and associates illustrates, can significantly modify the cardiovascular actions of concomitantly administered anesthetics.

One intriguing aspect of these interactions is that they appear to be complex and difficult to predict from the pharmacology of the individual agents: 2 plus 2 sometimes seems to equal 3 or 5. For example, in Hill's study N_2O added to 0.8 percent halothane gave beta-adrenergic-like effects but addition of N_2O to 1.6 percent halothane resulted in changes reminiscent of alpha-adrenergic stimulation. Dr. Hill gave evidence that part of these responses resulted from the progressive beta-adrenergic stimulatory effects of prolonged halothane administration at light (1 MAC) but not deeper levels of anesthesia. Indeed, at 1 MAC halothane the cardiac output and heart rate after N_2O were greater than the pre-N_2O control values with no such evidence of the effect of duration of anesthesia appearing at 1.5 or 2.0 MAC.

In contrast, we have found that considerable beta-like stimulation developed with time at deeper levels of prolonged halothane anesthesia with[1] or without N_2O.[2] However, in our studies the depth of anesthesia was varied at intervals and perhaps the sojourns at lighter levels uncovered or induced the beta-like stimulation at deeper levels. This would agree with Hill's suggestion that N_2O antagonized an apparent beta-adrenergic effect of 1.2 or 1.6 percent halothane. It may be that avoidance of lighter levels of anesthesia would preclude the development of increasing beta sympathetic activity.

One further point may be worth noting. In another of our studies where we acutely added 70 percent N_2O to a constant background of halothane, the sympathetic response seen appeared to depend in part on how soon you looked after starting the N_2O.[3] Peak changes occurred at 10 to 12 minutes and were decreasing at 15 minutes. Thus it appears that at least a portion of the sympathetic response to N_2O "fatigues" or

adapts rather rapidly. This may have contributed to the results obtained by Dr. Hill.

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During the first 3 days after admission, 29 patients had elevation of serum enzymes which may be derived from cardiac muscle, particularly CPK, which was increased 6-fold, compared to 2-fold increases in HBDH, GOT, and LDH. Only 5 of these patients had ECG evidence of recent myocardial infarction. Patients with elevated serum CPK had a 2-fold higher incidence of ST-segment depression, T-wave inversion, conduction defects and atrial fibrillation than those with normal CPK, and a mortality of 66 percent, compared to 30 percent. Of 41 patients who died, 49 percent had elevated serum CPK, compared to 15 percent of 59 patients who survived. These differences were significant ($p < 0.01$). Serum CPK was more frequently helpful than the ECG in evaluating the extent of cardiac damage and in predicting mortality. Patients with acute cerebrovascular accident should have repeated measurements of serum CPK and the ECG, and should be monitored for arrhythmias. *(Dimant J, Grob D: Electrocardiographic changes and myocardial damage in patients with acute cerebrovascular accidents. Stroke 8:448-455, 1977)*

Epidural Anesthesia and the Lateral Position

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The effect of the lateral position on the onset, maximum spread, and duration of anesthesia were observed using a standardized epidural anesthetic technic. Anesthesia appeared 2 minutes earlier on the dependent side, spread 2 spinal segments higher, and lasted 75 minutes longer. These results support the clinical practice of placing the patient in the lateral position with the operative side dependent for induction of epidural anesthesia.

Key Words—ANESTHETIC TECHNIC, peridural.

ALTHOUGH many factors are known to affect the spread of local anesthetic solutions injected into the epidural space, the effects of gravity have not been completely studied. Bromage, for example, has shown that increased volumes are required in order to achieve a given segmental level when the patient is in the sitting position,[1] but there is no information on the effect of the lateral position, even though Bromage has suggested it is important when small volumes of fast-acting local anesthetics are used.[2] By utilizing a standardized epidural technic, we eliminated many of the variables known to influence, or suspected of influencing, the spread of local anesthetic solutions in the epidural space and so were able to study the effect of the lateral position on epidural anesthesia.

MATERIALS AND METHODS

All patients were ASA physical status I or II undergoing elective surgery predominantly on one side of the body. They were positioned on their sides on a horizontal operating table with the operative side dependent. After the back was cleaned and draped, the L_{3-4} interspace was identified and an 18-gauge thin-walled Hustead needle was introduced in the midline and advanced until the epidural space was identified by loss of resistance to injection. The bevel was then pointed cephalad and 20 ml of 0.75 percent bupivacaine without epinephrine was injected slowly (at a rate of about 1 ml/sec). The patient was left in the lateral position with the table horizontal for at least 15 minutes, during which time the onset of anesthesia was observed by noting the loss of sharpness of pinprick according to Foerster's dermatome map.[3] Afterward, in the recovery room, the regression of anesthesia was followed by the same technic but with the patient supine.

RESULTS

The patients consisted of 5 females and 7 males with a mean age of 48 years (range

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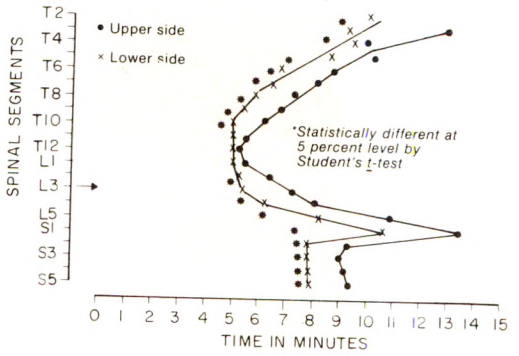


FIG 1. Time of onset of anesthesia after epidural injection of 20 ml of 0.75 percent bupivacaine with the patient in the lateral position

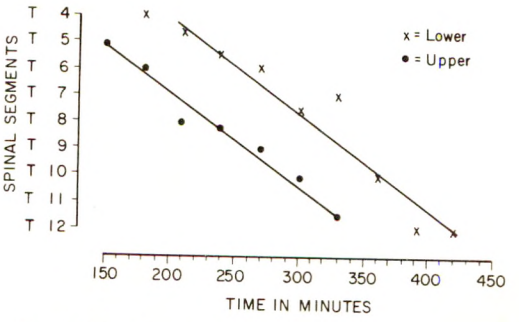


FIG 3. Duration of anesthesia on the upper and lower sides of the body when initial injection was made in the lateral position

17 to 67 years), a mean height of 165 cm (range 145 to 180 cm), and a mean weight of 70 kg (range 49 to 100 kg). None of the patients had an intra-abdominal tumor or evidence of arteriosclerosis. Times of onset of anesthesia are summarized in fig 1. The dependent segments had a more rapid onset at every level; in the low thoracic area the difference was only about 1 minute, while in the low lumbar and sacral areas, there was a 2- to 4-minute differential, and in the high thoracic area a 2- to 3-minute differential. This differential only achieved significance at the 5 percent level above T_{10} and below L_3 according to Student's *t*-test. Not all patients had anesthesia extending above T_6; those who did tended to have a rapid onset to a high level of anesthesia, which explains the apparent discontinuity of the onset in the high thoracic segments. The maximum spread of anesthesia on the upper and lower sides is shown in fig 2. In 8 of the 12 patients the level of anesthesia extended 2 spinal segments more cephalad on the dependent side than it did on the upper side. Data on the regression of anesthesia are shown in fig 3. Anesthesia on the dependent side at a given dermatomal level lasted an average of 75 minutes longer than on the upper side.

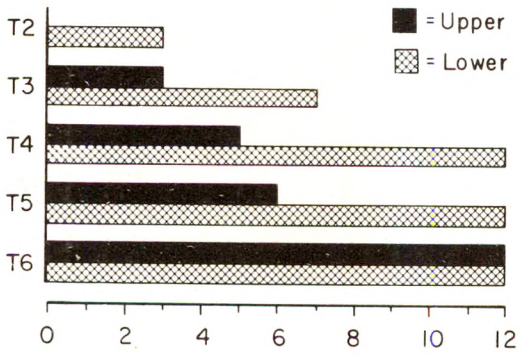


FIG 2. Maximum spread of anesthesia on the lower (dependent) and upper sides of the body following injection of 20 ml of 0.75 percent bupivacaine in the lateral position

DISCUSSION

The patients remained on their sides for at least 15 minutes after epidural injection. Within this time the spread and onset of epidural anesthesia was complete (fig 1), and thus we can assume that local anesthetic fixation had occurred and the influence of gravity operative during these 15 minutes had had its full effect. By standardizing our epidural technic, we hoped to minimize the influence of nonpostural variables. This we readily achieved for volume and concentration of local anesthetic, site of injection, rate of injection, and direction of the bevel during injection. The range of patient height was large, but the influence of height on the spread of epidural anesthesia is known to be slight.[1] The decreased volume required with increasing age to achieve a given segmental level is well recognized.[1,2] However, the maximum spread after our constant volume injection showed a remarkably small range of the upper level reached (fig 2), due no doubt in part to the fact that all but 4 of our patients were aged 45 to 60 years.

Gravity played a definite role when the patient was in the lateral position during injection; the dependent side had a more rapid onset to a higher level and a longer duration of anesthesia. In addition, although this was not quantified, we had the clinical impression that motor block was more intense on the dependent side. The magnitude of these effects is of interest. With spinal anesthesia the effect of position is of paramount

clinical importance, but with epidural anesthesia an onset of anesthesia that takes 2 minutes longer and is 2 spinal segments lower on the upper side is rarely of major clinical importance. A loss of 75 minutes duration is, however, significant, either in providing anesthesia for prolonged surgery or in achieving the benefits of postoperative analgesia.

We conclude, therefore, that it is good clinical practice to perform an epidural injection with the patient in the lateral position with the surgical side dependent and to let the patient remain on that side for 15 minutes. This may permit a slightly smaller volume of anesthesia to be used to achieve a given level on the side of surgery, but, more importantly, it will increase the duration of anesthesia on the dependent side by 1 hour or more.

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In 23 asthmatic children with severe sudden bronchospasm, baseline values for peak expiratory flow rate were less than 25 percent of those predicted. Three methods of administering isoproterenol hydrochloride (hand-held Freon-propelled nebulization, continuous nebulization, and intermittent positive-pressure breathing [IPPB]) were compared and found to be similar in reversing the bronchospasm ($p = 0.22$). Therapy with IPPB did not offer any advantage over simple nebulization in patients with severe, reversible airway obstruction. *(Loren M, Chai H, Miklich D, et al: Comparison between simple nebulization and intermittent positive-pressure in asthmatic children with severe bronchospasm. Chest 72:145-147, 1977)*

Neonatal Gastric pH

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The pH of gastric juice, obtained 3 to 4 minutes after birth in 158 unselected neonates, varied between 7.5 and 8.5 in 8 meconium-containing specimens and ranged from 1.4 to 7.8 in 150 meconium-free samples. In mature infants of the latter group, pH was (1) significantly lower after vaginal delivery than after cesarean section; (2) tended to be lower after section preceded by labor than after elective section; and (3) was lowest after precipitate delivery. In premature infants, pH was above 7 regardless of mode of delivery.

There was no correlation between neonatal gastric pH and pH of simultaneously obtained maternal gastric juice, pH of amniotic fluid, pH of cord blood, duration of rupture of membranes, birth weight, or Apgar score. It was concluded that the mature human fetus produces gastric acidity in response to stresses associated with labor and vaginal delivery.

The possibility of a low gastric pH and the resultant pulmonary damage if aspirated must be considered in the initial care of the newborn with poor muscle tone or reflex activity as well as in the anesthetic management of neonates undergoing emergency surgery.

Key Words—GASTROINTESTINAL TRACT, stomach. ACID-BASE EQUILIBRIUM, gastric pH. ANESTHESIA, obstetric. ANESTHESIA, pediatric.

A STUDY by Datta et al[1] on lidocaine levels in neonatal gastric juice following maternal extradural analgesia revealed larger amounts of the drug in infants delivered vaginally than in infants delivered abdominally. This finding was attributed to the lower gastric pH observed in the former group. We became interested in the factors determining neonatal gastric pH and have measured gastric pH in 158 unselected neonates, 115 of whom were born vaginally and 43 by cesarean section.

METHOD

Gastric juice was suctioned into a clean 20-ml deLee trap via a 2-mm orogastric catheter 3 to 4 minutes after birth, that is, after completion of the initial care of the neonate but before assignment of the 5-minute Apgar score. Usually 5 ml, but at least 3 ml, of gastric juice were collected; however, no attempt was made to empty the stomach. The pH was measured within 5 minutes using a Corning electrode. Whenever possible, amniotic fluid was also obtained for pH measurements, and umbilical vein and artery bloods were sampled from a double-clamped piece of cord for determination of acid-base data. In 10 women in whom an oral antacid had not been administered during labor or prior to cesarean section, maternal gastric juice was collected for pH measurement by means of an orogastric tube at the time of parturition.

Analysis of variance and coefficient of correlation were used for the statistical analyses.

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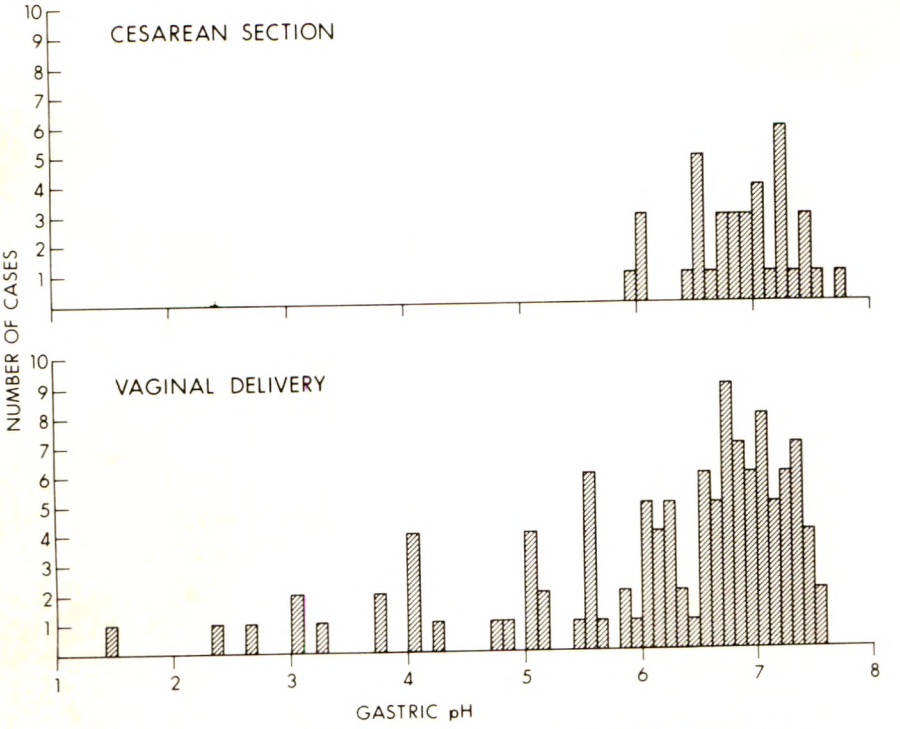


FIG 1. Histogram of pH of meconium-free gastric juice in 150 neonates

RESULTS

Gastric juice was contaminated with meconium in 8 cases (2 vaginal deliveries, 6 cesarean sections), and pH varied between 7.5 and 8.5 (mean 7.94 ± 0.32); these cases were excluded from analysis. Gastric juice was clear and pale-white, ie, without meconium, in 150 cases (113 vaginal deliveries, 37 cesarean sections), and pH ranged from a low of 1.4 to a high of 7.8; these cases form the basis of this report.

In 130 term and late preterm (born after the 34th week of gestation) infants, gastric pH values were significantly (<0.05) higher following cesarean section than following vaginal delivery (fig 1) and tended to be higher after elective sections than those preceded by labor (table). However, gastric pH was highest—above 7—in all 20 early preterm infants, that is, infants born at or before 34 weeks of gestation, regardless of mode of delivery, ie, vaginal (17) or ab-

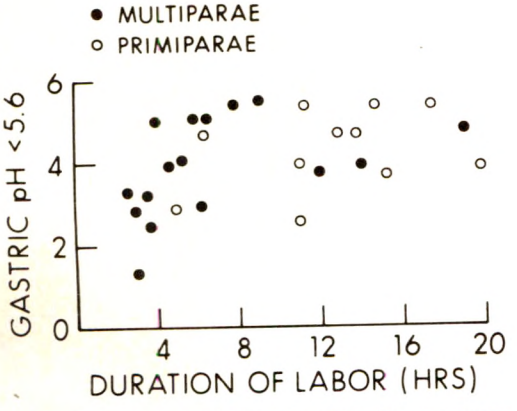


FIG 2. Low neonatal gastric pH values were prevalent following rapid labor and precipitate delivery

TABLE

pH at Birth of Meconium-Free Gastric Juice in 150 Neonates

Gestational age	No.	Gastric pH Range	Gastric pH Mean	SD
Early preterm		7.1-7.8	7.04*	0.02
Term and late preterm	130	1.4-7.6	6.21*	1.18
Vaginal delivery	96	1.4-7.6	6.00†	1.29
Cesarean section	34	5.9-7.4	6.79†	0.41
Elective	14	6.0-7.4	6.97	0.39
Emergency	20	5.9-7.4	6.69	0.46

*0.001
†0.05

dominal (3) (table). The lowest pH values were found following rapid labor and precipitate delivery (fig 2). Although no statistically significant correlation was discernible between gastric pH and duration of rupture of membranes ($r = -0.10$) or duration of the 2nd stage of labor ($r = -0.19$ in multiparae and $+0.18$ in primiparae), cases with low gastric pH tended to be associated with short periods of ruptured membranes and rapid 2nd stages. There was also no correlation between gastric pH and cord blood pH, cord blood base deficit, Apgar score, birth weight, or method of anesthesia (spinal, extradural, or pudendal block, inhalational analgesia, endotracheal anesthesia, or no anesthesia).

All amniotic fluids had a pH between 6.9 and 7.5. In 12 cases in which amniotic fluid was sampled at the time of rupture of membranes and again at delivery, there was no change in the pH value.

Analysis of the 10 cases in whom the maternal gastric pH had not been modified iatrogenically revealed a lower maternal than neonatal pH in every instance, but there was no consistent difference between the 2.

DISCUSSION

The question arises as to the origin of the acidity in neonatal gastric juice. The role of amniotic fluid was ruled out by the aforementioned findings of unchanging amniotic fluid pH values close to the pH of maternal arterial blood as well as by the lack of correlation between duration of rupture of membranes and neonatal gastric pH. Had the swallowing of amniotic fluid been a determining factor, the lowest pH values would have occurred with the longest periods of ruptured membranes, as amniotic fluid would have been unavailable for swallowing by the fetus.

Transfer of maternal gastrin to the fetus is unlikely for 4 reasons: First, the large size of the gastrin molecule (approximately 2,100)[2] makes placental transfer improbable. Second, in the study by Roberts and Shirley,[3] maternal gastric pH values were in the same ranges during vaginal and abdominal deliveries, with and without labor. Third, all premature infants in our series had gastric pH values above 7 regardless of the mode of delivery. And fourth, we found no consistent difference between maternal and neonatal gastric pH in simultaneously obtained samples.

We conclude, therefore, that the mature human fetus produces gastric acidity in response to stresses associated with labor and vaginal delivery. Gastric secretion is regulated by both nervous and hormonal mechanisms, the nervous regulation being effected primarily through the parasympathetic fibers of the vagus nerves.[4,5] Fetal vagal reflex activity has been demonstrated by electronic heart-rate monitoring.[6] We postulate that pressure phenomena, most likely on the fetal head, initiate vagal stimulation and gastric secretion. In this context, it is interesting that the only 2 instances of "early" fetal heart rate deceleration in our series occurred in infants with gastric pH below 4. Early deceleration is thought to be due to fetal head compression.[7]

Meconium consists of bile, bile acids, and swallowed amniotic fluid containing lanugo, vernix caseosa, and epithelial cells; varying amounts of intestinal and pancreatic secretions are also present.[8] The pH of meconium is, generally, above 7.5 because of the alkalinity of bile and pancreatic juice. Obviously, meconium-contaminated gastric juice is unsuitable for a pH study.

The finding of absent gastric acidity in infants born before 34 weeks of gestation resembles the results of a recent study showing a sharp increase in levels of cortisol in amniotic fluid after the 34th week. This was interpreted as a rise in cortisol production by fetal adrenal glands which, in turn, appears to be responsible for the induction of the process of lung maturation.[9]

From a clinical point of view, it is noteworthy that the gastric pH of the newborn infant may be below 3, thus facilitating the development of chemical pneumonitis should pulmonary aspiration of stomach contents occur. For this reason, we recommend gastric aspiration in all neonates with poor muscle tone or poor reflex activity. Furthermore, the possibility of a low gastric pH must be considered in the anesthetic management of neonates undergoing emergency surgery, particularly since earlier investigations have revealed a significant increase in gastric acidity during the first 6 hours of life.[10,11] In 53 newborns studied by Ebers et al,[10] mean gastric pH was 5.4 at 15 to 60 minutes after birth; specimens taken 1 hour later showed a pH of 3.1 with a further decrease to 2.2 by 5 to 6 hours.

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Fifteen hundred consecutive preoperative chest x-rays in frontal and lateral views were obtained on patients newborn to 19 years of age. In 7.5 percent of patients there was at least 1 roentgenographic abnormality, with 4.7 percent of patients demonstrating a totally unsuspected significant abnormality. In 3.8 percent of patients surgery was either delayed or canceled, or the anesthetic technic was altered as a result of the roentgenographic finding. It is suggested the routine preoperative chest film is justified if the film is evaluated before surgery and the results clinically followed up. *(Sane SM, Worsing RA, Wiens CW, et al: Value of preoperative chest x-ray examinations in children. Pediatrics 60:669-672, 1977)*

Tetanic Fade and Post-Tetanic Tension in the Absence of Neuromuscular Blocking Agents in Anesthetized Man

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Frequency and time dependent changes in neuromuscular transmission were examined in 30 patients undergoing elective minor surgical procedures not requiring the use of muscle relaxants. Anesthesia was induced with sodium thiopenthal and maintained with N_2O-O_2 and fractional doses of meperidine or fentanyl.

Neuromuscular function was measured by recording the force of thumb adduction evoked by supramaximal stimulation of the ulnar nerve at the wrist. Single stimuli were applied every 2.5 seconds as square pulses of 0.1-millisecond duration. Tetanic trains of 10-second duration ranging from 10 Hz to 400 Hz were used.

From analysis of present data, criteria for normal responses to 10-second tetanic trains of varying frequencies were established. At a frequency of 30 Hz, the tetanic response is fully maintained and followed by post-tetanic potentiation; at a frequency of 50 Hz, both tetanic and post-tetanic responses are maintained; at a frequency of 100 Hz, there is tetanic fade, followed by a post-tetanic depression of the single indirect twitch responses.

It is concluded that frequency and duration of indirect stimulation are the most important factors in using tetanic maintenance and post-tetanic events in assessment of recovery from neuromuscular block.

Key Words—NEUROMUSCULAR TRANSMISSION, tetanic stimulation. MEASUREMENT TECHNICS, neuromuscular blockade.

THE accuracy of methods for evaluation of the state of neuromuscular transmission in anesthetized man has been studied by Katz,[1,2] Gissen and Katz,[3] and Epstein and Epstein,[4] and recently reviewed by Ali and Savarese.[5] Criteria proposed for recovery from neuromuscular block include tetanic maintenance with frequencies above 100 Hz. This criterion was based on experimental work of Paton and Waud,[6] and Waud and Waud,[7] and recently reviewed by Miller.[8]

In mammalian neuromuscular preparations fatigue of neuromuscular transmission develops during indirect stimulation of motor nerve even in the absence of neuromuscular blocking agents. Transmission fatigue has been demonstrated as a frequency dependent event in classical work of Wedensky[9] and of Rosenblueth et al.[10]

The purpose of this study was to explore the effect of stimulation frequency and of stimulus duration on tetanic maintenance in

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the absence of neuromuscular blocking agents in anesthetized man.

METHOD

Thirty healthy adults of both sexes with a mean age of 40 (range 17 to 65) were studied during elective minor surgical procedures not requiring the use of muscle relaxants. Informed consent was obtained from all patients. Premedication consisted of atropine 0.005 mg/kg and meperidine 0.5 to 1 mg/kg IM 1 hour preoperatively. Anesthesia was induced with sodium thiopenthal 2 to 3 mg/kg and maintained with a 4:2 L/min N_2O-O_2 mixture supplemented with incremental doses of meperidine 1 mg/kg (12 patients) or fentanyl 0.005 mg/kg (18 patients). Ventilation was assisted or controlled; $Paco_2$ was maintained within normal limits. All patients were normothermic. The trachea was intubated after local spray of 4 percent lidocaine (160 mg) and a single IV dose of succinylcholine 0.5 mg/kg if necessary. In 9 patients who required succinylcholine for intubation, control twitch and tetanus at 30 Hz/10 sec and 100 Hz/10 sec were obtained on 2 occasions: prior to administration of succinylcholine, and 15 to 30 minutes after intubation, when twitch and tetanus had returned to original values. Only those patients were included in the study where postsuccinylcholine control was identical with original control. Patients who received succinylcholine for intubation showed no difference in response from patients who had not received the relaxant.

Neuromuscular function was measured by recording the force of thumb adduction evoked by supramaximal stimulation of the ulnar nerve at the wrist. The tension developed in adductor pollicis muscle in response to ulnar nerve stimulation was measured with a Grass linear force-displacement transducer (FT 10) and recorded on a polygraph. The ulnar nerve was stimulated with a pair of subcutaneous needle electrodes via a Grass stimulus isolation unit (SIU 5). The SIU 5 and a Grass S 44 stimulator were incorporated in a specially designed unit with automatic switching from single impulse stimuli to tetanic trains of varying frequencies.

Stimulating Parameters — Stimuli were applied every 2.5 seconds as square pulses of 0.1-millisecond duration. Ten-second tetanic trains of varying frequencies were used in random order. Tetanic frequencies varied from 10 Hz to 400 Hz. Intervals between each train were 5 minutes for the low frequencies and 10 to 15 minutes for higher frequencies. No tetanus was repeated until the twitch tension returned to the pretetanic value. The first post-tetanic stimulus always followed the tetanic train by 2.5 seconds.

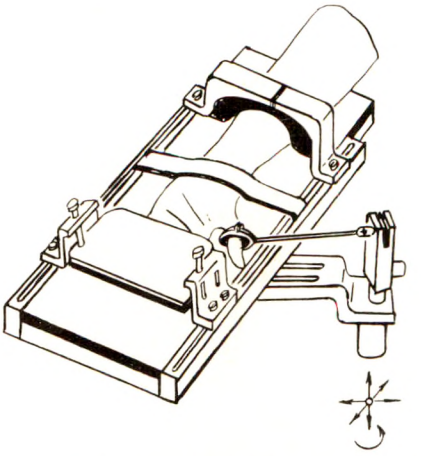


FIG 1. A special adjustable transducer holder with a Grass FT-10 force-displacement transducer in place for recording of thumb adduction. The thumb is placed in an adjustable hook connected by a steel rod to the transducer at a 90° angle. The hand and forearm are immobilized on a special arm board to which the transducer holder can be attached from either side.

Technic of Hand Fixation — Figure 1 shows a transducer holder specially designed and constructed to measure isometric contraction of the adductor pollicis muscle. The holder is attached to an arm board on which the hand and the forearm are immobilized. The position of the transducer holder is adjustable in all directions, as indicated. The thumb is placed in full abduction in an adjustable hook, connected by a steel rod to the transducer at a 90° angle. Since the transducer is extremely sensitive to the di-

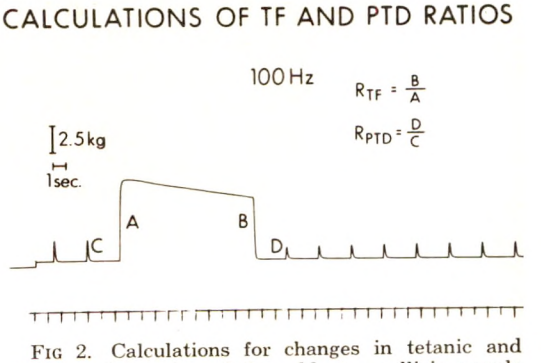


FIG 2. Calculations for changes in tetanic and post-tetanic tension of the adductor pollicis muscle during indirect stimulation of the ulnar nerve at the wrist. See text for explanation.

rection of the applied force, the transducer cantilever was always aligned parallel to the fully abducted thumb and perpendicular to the point of insertion of the muscle (the base of first phalanx of thumb on ulnar side.) Thus the force of adduction was applied in the axis of the transducer. The transducer was calibrated prior to each study. A constant resting tension (preload) of 400 to 500 g was applied in each study. Maximum tetanic tension was 3 to 4 times that of single twitch tension. The speed of the recording paper was increased to detect any waning of the tetanic tension.

Analysis of Data—The calculations made for changes in tetanic and post-tetanic tension responses are shown in fig 2. The following were evaluated as functions of frequency: tetanic maintenance, tetanic fade (TF), post-tetanic potentiation (PTP), and post-tetanic depression (PTD). Shortly after the onset of 10-second tetanic train, a maximum tension develops and is either maintained (up to 50 Hz), or there is a gradual fall in tension to a minimum at the end of the train. We expressed the fade of TF as the ratio between the tension at the end and the tension at the beginning of tetanus (R_{TF} = B/A). In a similar manner, we expressed the increase or decrease in post-tetanic tension (PTP or PTD) as the ratio between the first post-tetanic twitch tension and the last pretetanic twitch tension (R_{PTD} = D/C). Mean values for each parameter were determined and frequency response curves constructed. Each data point on the frequency response curves represented the mean of 30 determinations. Each determination represented 1 response to 1 frequency chosen by random order. Reproducibility of the responses to various frequencies of stimulation was established in a previous unpublished study. Data were analyzed for statistical significance by Student's *t*-test, with $p<0.05$ considered significant.

RESULTS

Normal adductor pollicis muscle under steady state conditions in anesthetized man shows reproducible frequency responses to tetanic stimulation. Typical examples of recordings from the present study are shown in fig 3.

From analysis of the data, criteria for normal responses to 10-second tetanic trains of varying frequencies were established: (1) at 30 Hz, tetanic tension is well maintained, followed by PTP; (2) at 50 Hz, both tetanic and post-tetanic tensions are maintained; and (3) at 60 Hz and above, tetanic and post-tetanic tensions are not maintained. The higher the frequency of tetanic stimulation, the more pronounced TF and PTD. The recovery time of post-tetanic tension is also frequency dependent.

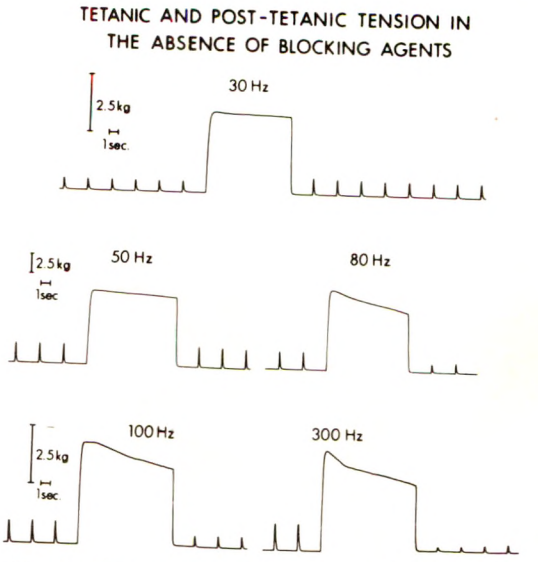


FIG 3. Typical examples of mechanical recordings during 10-second tetanic trains: 30 Hz with well-maintained tetanic tension and PTP; 50 Hz with maintained tetanic and post-tetanic tension; 80 Hz, 100 Hz, and 300 Hz with frequency-dependent TF and PTD.

Peak Tetanic Tension in Normal Adductor Pollicis Muscle — The relationship between stimulation frequency and peak tetanic tension is shown in fig 4. The maximum tension at the beginning of tetanic train was reached between 30 and 50 Hz. The mean value from the responses of 30 patients at the optimal frequency was 7.1 kg ± 2.2 SD ± 0.6 SE and did not change significantly up to 300 Hz. At 400 Hz the tension peak decreased.

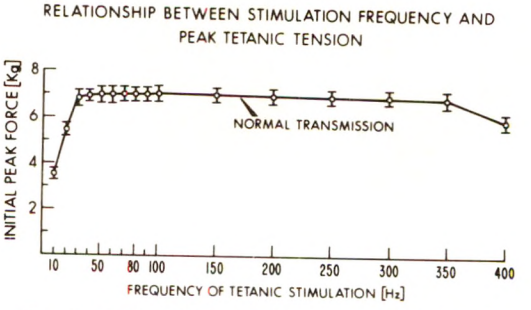


FIG 4. Peak tetanic tension in normal adductor pollicis muscle. Vertical lines represent ± SE.

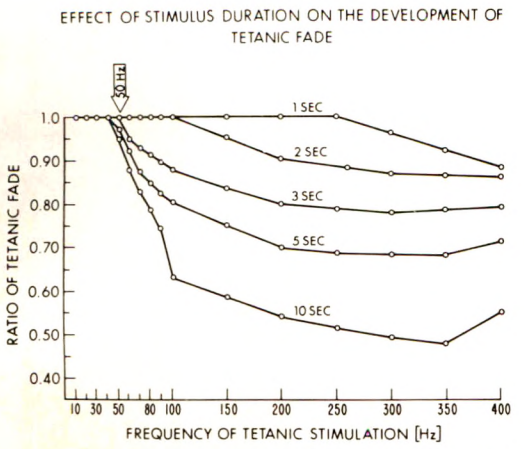


FIG 5. Effect of tetanic stimulus duration on the development of TF in the absence of blocking drugs. At the same frequencies of tetanic stimulation, waning of tetanic tension becomes more pronounced as the duration of tetanic train increases.

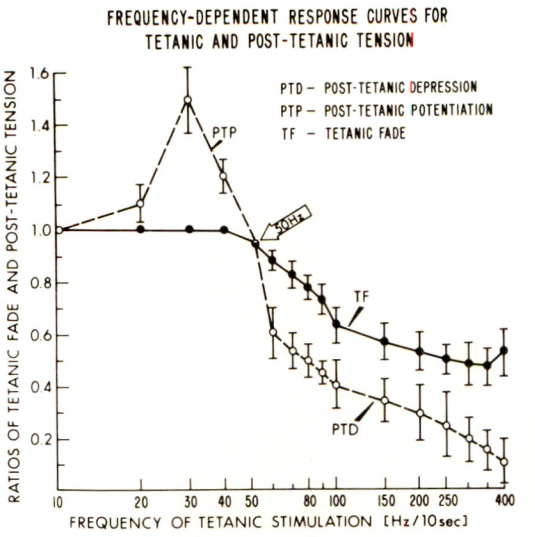


FIG 6. Effect of frequency of indirect stimulation on tetanic and post-tetanic tension in the absence of blocking drugs. Duration of tetanic trains is 10 seconds. Vertical lines represent ± SD.

Effect of Stimulus Duration on the Development of TF in the Absence of Blocking Drugs—With increasing duration of tetanic train at the same frequencies, TF became more pronounced (fig 5). During a 1-second tetanic train, mean tension was fully maintained up to 300 Hz; during a 2-second train, tension was maintained up to 150 to 200 Hz; during a 3-second train, tension was maintained up to 80 to 100 Hz; during a 5-second train, tension was maintained up to 70 Hz; and during a 10-second train, tetanic tension was maintained only up to 50 Hz.

Effect of Stimulation Frequency on Tetanic and Post-Tetanic Tension in the Absence of Blocking Drugs — Frequency-dependent response curves for the mean tetanic and post-tetanic tension are shown in fig 6 where ratios of tetanic maintenance, TF, PTP, and PTD are plotted as a function of increasing stimulation frequency during 10-second tetanic trains. Tetanic fade developed above 50 Hz and increased directly with frequency; at 400 Hz the ratio of TF increased due to the decrease in peak force of tetanic tension. Post-tetanic tension increased with frequencies of 20 to 40 Hz, with maximum PTP at 30 Hz (R_{PTP} = 1.5 ± 0.15 SD). Mean ratio of PTP from frequencies of 20 to 40 Hz was 1.2. The 2 curves cross at 50 Hz. At this frequency tetanus is maintained (R_{TF} = 0.96 ± 0.05 SD) and there is no significant difference between the pre- and post-tetanic tension (R_{PTD} = 0.99 ± 0.01 SD). Above 60 Hz the PTD follows the TF. Correlation between TF and PTD (frequencies of 60 to 300 Hz) follows a linear relationship. This correlation was highly significant (correlation coefficient R = 0.98). In general, in man, with increasing frequencies of tetanic stimulation above physiological range, we observed parallel decreases in tetanic and post-tetanic tensions.

DISCUSSION

Changes in skeletal muscle responses to indirect stimulation of motor nerve are determined by the factors controlling release of the transmitter from the motor nerve terminals. The amount of acetylcholine liberated by a single nerve impulse is only a fraction of the amount available for release. The amount liberated during continuous stimulation is influenced by the extent to which mobilization from the transmitter stores is able to keep up with release.[11]

In mammalian neuromuscular preparations, in the absence of blocking drugs, as the frequency of indirect stimulation increases, a typical picture of Wedensky inhibition[12] results. In the presence of curare, Wedensky inhibition occurs at relatively low frequencies of stimulation. Direct stimulation of a fully curarized muscle does not show Wedensky inhibition. Thus the phenomenon of Wedensky inhibition represents events occurring at the neuromuscular junction. Both an excess and a deficiency of acetylcholine may lead to depression of muscular responses.

The depression or failure of transmission from nerve to muscle during fatigue produced by indirect stimulation was localized to the motor end plate almost a century ago.[13] The results from experimental work of Luco and Rosenblueth[14] eliminated both muscle and nerve as the site of fatigue. The cholinergic mechanism of transmission fatigue is quite complex. Depletion of acetylcholine appears to be the mechanism of transmission fatigue in prolonged indirect stimulation.[15] Wedensky inhibition in a fatigued preparation can be explained on the basis of a rapid decline of liberated transmitter in successive nerve volleys. As acetylcholine concentration becomes subthreshold for more and more of the junctions, contractions of the muscle as a whole gradually become smaller. In addition, there is a presynaptic failure of propagation, located probably in the fine terminal filaments of the motor nerve.[16-18]

Bowman and Webb[16] in a recent study suggested that acetylcholine, in addition to evoking the end-plate potential, acts on nonmyelinated nerve terminals in a positive-feedback mechanism that mobilizes the transmitter to keep pace with release during high frequencies of stimulation. The authors also proposed that waning of tetanic tension which reflects waning of transmitter output during high-frequency stimulation is largely a consequence of prejunctional cholinoceptor blockade. Hubbard and associates[17] investigated the presynaptic effects of acetylcholine. They concluded that acetylcholine depolarizes nerve terminals at a site more proximal than the site of release of transmitter, presumably the adjacent nodes of Ranvier. Riker,[18] in studying the actions of acetylcholine on mammalian motor nerve terminals, demonstrated that acetylcholine initially excites and then blocks neuromuscular transmission. Since depolarization of motor nerve terminal by acetylcholine has been documented, Riker proposed that an initial intense terminal depolarization could also block the propagation of an evoked nerve response.

In designing the present study, the main consideration was to stimulate the system to a degree that allows recording of responses that reflect transmitter dynamics. Higher frequency and longer duration of tetanic stimulation stress the system to greater degrees than do the lower frequency of stimulation or shorter duration of tetanus. Thus transmission fatigue may become evident. We observed that with increasing frequency of indirect stimulation above physiological range, tetanic tension decreased and was followed by PTD of single twitch responses. This depressant effect increases with increasing frequencies of stimulation. With stimulation frequencies within physiological range, tetanic tension is well maintained and followed by PTP. The maximum PTP was observed with 30 Hz after 10-second tetanus. No PTP was seen below 10 Hz or above 50 Hz.

Our present data suggest that:

1. Tetanic maintenance with frequencies above 50 Hz, unless used for 1 to 2 seconds, is not a reliable criterion of recovery from neuromuscular block.

2. Tetanic trains of 30 Hz could lead to erroneous conclusions in evaluation of neuromuscular block, since reproducible PTP develops after this frequency even in the absence of blocking drugs.

3. Tetanic trains of 50 Hz applied for 10 seconds are a good choice for evaluation of recovery from neuromuscular block, since in the absence of blocking drugs tetanic and post-tetanic tensions are maintained.

4. Tetanic trains above 100 Hz, unless used for 1 second, can be misleading since tetanic fade develops even in the absence of blocking drugs.

Two findings from this study are of special interest. One is the origin of PTP in the absence of blocking drugs. Standaert[19] studied the origin of PTP in soleus (slow) and gastrocnemius (fast) muscle of cats and found different mechanisms for slow and fast muscle. Soleus PTP is predominantly a neural event. High-frequency stimulation of soleus nerve causes subsequent responses to a single stimulation to become repetitive. This post-tetanic repetitive firing originates in the motor-nerve terminals and is then transmitted to the muscle, causing PTP. Gastrocnemius PTP is predominantly a muscle phenomenon and occurs even in the presence of curare during direct stimulation. However, both mechanisms may operate in both muscles, but in different degree. Both muscles also show a significant difference in PTP frequency dependence. Soleus PTP increases with frequency and with duration of stimulation. The maximum potentiation occurs after 400 Hz applied for 10 seconds. In contrast, gastrocnemius PTP occurs after lower frequencies of stimulation with maximum potentiation produced by 100 to 200 Hz applied for 10 seconds.

Human muscle is mixed and the precise percentage of fiber type in adductor pollicis muscle is not known. Therefore, both mechanisms described by Standaert could be responsible for occurrence of PTP in the absence of blocking drugs in man.

The 2nd main finding of interest is the origin of PTD after a 10-second train. PTD in normal muscle stands in contrast to PTP seen in curarized muscle with the same frequencies of stimulation. Since previous studies in man used tetanic trains of 0.5 to 5 seconds duration, post-tetanic depressant effects on twitch tension in the absence of blocking drugs could not be detected. The loss of post-tetanic tension seen after high-frequency stimulation and its slow return could reflect time-dependent restoration of available transmitter stores in the motor-nerve endings. The depression of tetanic and post-tetanic tension seen after tetanic trains above 60 Hz increases with increasing frequencies of stimulation. The question arises as to whether TF and PTD could be sensitive technics for studying the effect of facilitatory and depressant drugs on neuromuscular transmission. Depending upon the nature of the drug studied, a shift in the frequency-response curve would be expected. To speculate on the answers to these questions is outside the scope of this study and needs further investigation.

In conclusion, our results demonstrated that in anesthetized man, in the absence of blocking drugs, with frequency of tetanic stimulation above 50 Hz and duration of tetanic trains above 1 to 2 seconds, a frequency-dependent TF develops. In addition, we found that after a 10-second tetanic train at 60 Hz and above, TF is followed by a frequency-dependent PTD of single twitch responses.

ACKNOWLEDGMENT

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Intravenous Potassium Chloride in Hypokalemic Dogs Pretreated with Digoxin

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The cardiovascular effects of IV potassium were evaluated in 12 dogs—6 controls that received no treatment prior to potassium administration and 6 experimental animals treated daily for 7 days with IV digoxin (0.05 mg/kg the first day and 0.01 mg/kg on subsequent days) and, to render them hypokalemic, concurrent IV furosemide (1.0 mg/kg/day). Anesthesia was then induced with thiopental and maintained with 1 percent halothane in N_2O-O_2 (3 L - 2 L) while respirations were mechanically controlled to maintain $Paco_2$ at 30 to 35 torr. Intravenous potassium chloride (KCl), 1.6 mEq/kg/hr for 1 hour, was then administered to each dog during an initial study; at least 7 days later KCl 3.2 mEq/kg/hr for 1 hour was infused during a 2nd study.

Experimental animals showed reduction of serum potassium from control levels of 4.39 ± 0.06 down to 3.75 ± 0.04 mEq/L ($p<0.001$) on the day of study, while the untreated dogs had a mean serum potassium level of 4.25 ± 0.06 mEq/L prior to each KCl infusion. The infusion of both doses of KCl in hypokalemic dogs increased cardiac output, heart rate, and stroke volume. No mortality was observed after infusion of 1.6 mEq/kg KCl in either control or pretreated animals. Three of 6 pretreated dogs survived the infusion of 3.2 mEq/kg KCl, while there were no survivors in the control group. There were no significant changes in the serum potassium concentrations or the absolute urinary $[K]^+$ in either the experimental or in the control group following infusion of 1.6 mEq/kg KCl. Animals in the experimental group that survived the 3.2 mEq/kg KCl infusion showed peak serum $[K]^+$ of 8.0 ± 0.71 mEq/L and urinary excretion of 15.1 ± 5.9 mEq at the end of KCl infusion, while nonsurvivors showed corresponding values of 12.3 ± 1.3 mEq/L and 6.7 ± 2.1 mEq, respectively. The results suggest that hypokalemic and digoxin-pretreated animals exhibit a positive inotropic response to intravenous KCl and may also be more tolerant to the toxic effects of IV KCl.

Key Words—IONS, potassium.

NORMAL myocardial rhythmicity and contractility are dependent upon proper maintenance of transmembrane potassium concentration gradients within cardiac cells. Myocardial dysfunction can result from hyperkalemia as well as hypokalemia. Many hypokalemic patients requiring surgery have been chronically treated with digitalis and diuretics. In emergency situations, potassium chloride (KCl) is sometimes infused in such patients to raise serum potassium levels to more normal values in order to minimize cardiac dysrhythmias during anesthesia. We have recently shown that acute

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infusion of KCl in dogs pretreated with furosemide may not be effective in treating the furosemide-induced hypokalemia and could be detrimental to the cardiovascular system.[1] The present study evaluates changes in serum potassium and sodium associated with daily IV administration of digoxin and furosemide in dogs. Intravenous KCl was then administered to untreated control dogs and to pretreated hypokalemic dogs while cardiovascular responses and serum and urinary levels of potassium and sodium were measured.

METHODS

Twelve male mongrel dogs weighing 17.5 to 26.0 kg were used for this study; 6 were untreated controls and 6 were experimental animals treated daily for 7 days with IV digoxin (0.05 mg/kg the first day and 0.01 mg/kg on subsequent days) and IV furosemide (1.0 mg/kg). On the 8th day IV KCl, 1.6 mEq/kg/hr for 1 hour, was administered during anesthesia to each dog during an initial study and followed at least 7 days later by KCl, 3.2 mEq/kg/hr for 1 hour IV, during a 2nd study. Serum potassium and sodium concentrations were measured in experimental animals daily during furosemide and digoxin pretreatment; in control animals these serum electrolytes were measured only once between each study, since we previously determined that they do not change significantly in healthy untreated dogs.

Intravenous thiopental 15 to 20 mg/kg was used to induce anesthesia and for endotracheal intubation, following which anesthesia was maintained with 1.0 percent inspired concentration of halothane in N_2O-O_2 (3 L - 2 L) while the lungs were mechanically ventilated to maintain $Paco_2$ of 30 to 35 torr. A catheter was inserted percutaneously into the femoral artery for continuous monitoring of arterial blood pressure and intermittent measurement of blood gases. Serum sodium and potassium concentrations were measured immediately before KCl infusion and every 30 minutes during the 180-minute study period, while urinary volume and urinary potassium and sodium concentrations were measured after 60 and 180 minutes. Lactated Ringer's solution, 10 to 15 ml/kg/hr, was given IV to all dogs throughout anesthesia. The arterial pulse contour was fed into a computer substation and analyzed to provide continuous measurements of cardiac output, stroke volume, heart rate, mean arterial pressure, and systemic vascular resistance by the method of Warner.[2,3] Lead II of the ECG and rectal temperature were continuously monitored.

When the preparation was stabilized 40 to 60 minutes after induction of anesthesia, KCl was infused IV over a period of 1 hour, using a Harvard syringe pump connected to a catheter placed in a forelimb vein. Preliminary studies infusing 0.8 mEq/kg/hr KCl demonstrated no significant cardiovascular effects or changes in renal excretion of potassium in either control or pretreated animals, similarly to our previous report with furosemide pretreatment only;[1] therefore, this study utilized only pharmacological doses of KCl, 1.6 and 3.2 mEq/kg in 40 cc of 5 percent dextrose in water, for the IV administrations. Serum and urinary $[Na]^+$ and $[K]^+$ were measured by an IL-143 flame photometer.

Statistical analysis was done using the *t*-test for paired and unpaired data. A probability of $p<0.05$ was considered statistically significant.

RESULTS

Daily administration of digoxin and furosemide for 7 days significantly reduced serum potassium from 4.39 ± 0.06 to 3.75 ± 0.04 ($p<0.001$) (table 1), while in untreat-

TABLE 1

Daily Plasma Levels in Dogs During Pretreatment with Furosemide (1 mg/kg) and Digoxin (0.05 mg/kg Day 1 and 0.01 mg/kg)*

	Days						
	1	2	3	4	5	6	7
K mEq/L	4.39 ±0.06	4.07† ±0.05	3.91† ±0.04	3.86† ±0.04	3.78† ±0.03	3.80† ±0.02	3.75† ±0.04
Na mEq/L	143.4 ±1.1	144.5 ±1.1	143.6 ±1.0	143.4 ±0.9	142.5 ±0.9	143.7 ±0.8	143.2 ±0.8

*Mean ± SE; $n = 12$.

†$p<0.001$; significantly different from day 1.

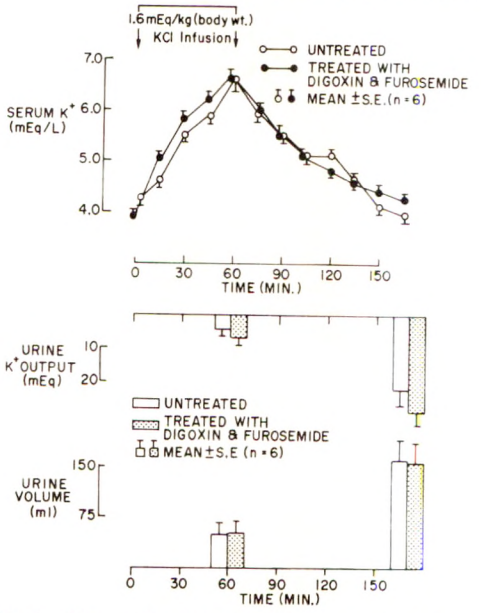


FIG 1. Serum K^+ concentration, urinary output, and urinary K^+ excretion in control and in experimental dogs during infusion of 1.6 mEq/kg/hr KCl for 1 hour.

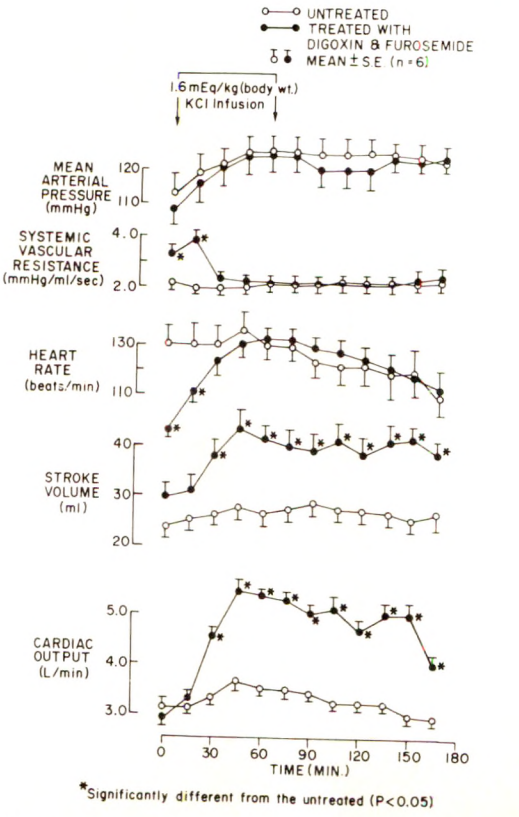


FIG 2. Changes in cardiac output, stroke volume, heart rate, peripheral vascular resistance, and mean arterial pressure during infusion of 1.6 mEq/kg/hr KCl for 1 hour in control and in pretreated animals.

ed control animals no change occurred over a similar period of time (4.32 ± 0.05 to 4.25 ± 0.06 mEq/L). No significant change in serum sodium was observed in either group.

Infusion of 1.6 mEq/kg KCl.—In hypokalemic animals serum potassium increased steadily during the 1-hour KCl infusion, reaching a peak value of 6.7 ± 1.0 mEq/L at the end of 1 hour, then declining to preinfusion values over the next 2 hours (fig 1). These changes in serum potassium were not statistically different from changes in the untreated control group (fig 1).

Serum sodium did not change throughout the study. Urinary excretion of potassium and urinary volume at the end of the infusion and at the end of the 3-hour study were comparable in both groups (fig 1).

Cardiac output increased in hypokalemic dogs when serum potassium levels exceeded 5.5 mEq/L and remained elevated even after serum potassium decreased to below 5.0 mEq/L (fig 2). In normokalemic control animals, on the other hand, similar elevations in serum potassium were not associated with significant increases in cardiac output. Increases in cardiac output were the result of increases in heart rate and stroke volume (fig 2). Preinfusion heart rates were significantly slower in the treated group than the untreated group. However, no significant difference in heart rate was observed between groups following 30 minutes of KCl infusion (fig 2). Mean arterial pressure did not change significantly in either group. Systemic vascular resistance was greater in the treated group than the untreated group before KCl infusion, but after 30 minutes of KCl infusion it decreased to values equal to those observed in untreated control animals and remained, as in the untreated control dogs, low through the rest of the study period (fig 2).

Changes in ECG associated with acute hyperkalemia were observed, and were the same in both untreated and furosemide-digoxin treated dogs.

Infusion of 3.2 mEq/kg KCl.—All 6 control animals succumbed to the 3.2 mEq/kg infusion of KCl, but 3 out of the 6 pretreated animals survived equal infusions of KCl. Nonsurvivors in the treated group showed earlier onset of dysrhythmias in comparison with the survivors (table 2).

TABLE 2
ECG Changes During KCl Infusion

K^+ infusion	Untreated		Furosemide-digoxin treated	
	Onset of nodal rhythm or ventricular extrasystole (min)	Onset of cardiac standstill or ventricular fibrillation (min)	Onset of nodal rhythm or ventricular extrasystole (min)	Onset of cardiac standstill or ventricular fibrillation (min)
1.6 mEq/kg	40 ± 16 (2/6)	———	48 (1/6)	———
3.2 mEq/kg				
Survived	———	———	45 ± 1 (3/6)	———
Succumbed	42 ± 5 (6/6)	54 ± 8 (6/6)	28 ± 6 (3/6)*	46 ± 6 (3/6)

*Significantly different from the untreated ($p<0.05$).

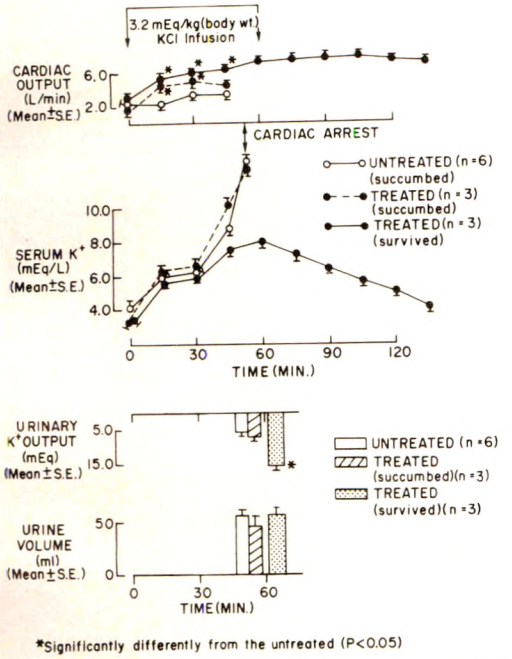


FIG 3. Serum K^+, cardiac output, urinary output, and urinary K^+ excretion rates associated with infusion of 3.2 mEq/kg/hr for 1 hour in control and in pretreated animals.

Mean serum potassium concentrations at the time of cardiac arrest were 13.8 ± 0.8 mEq/L in the untreated group ($n = 6$) and 12.3 ± 1.3 mEq/L in the treated group ($n = 3$). Three survivors in the treated group achieved a peak serum potassium concentration of 8.0 ± 0.71 mEq/L at the end of infusion, which then declined gradually toward the preinfusion level over the next 2 hours (fig 3).

Cardiac output in the treated group was significantly higher ($p<0.05$) after 15 minutes of infusion than it was in control animals. Survivors in the treated group continued to show increased cardiac output (fig 3).

There was no significant difference between urinary potassium excretion of the untreated group and the nonsurvivor treated group (fig 3). Urinary potassium output up to the end of the infusion period (60 minutes) among survivors of the treated group, 15.1 ± 5.9 mEq, was significantly higher than it was in untreated control animals up to the time of cardiac arrest (54 minutes), 6.7 ± 2.1 mEq (fig 3). There was no difference in the urinary output in the 2 groups over the same period (fig 3). Arterial blood gases remained stable throughout the studies.

DISCUSSION

Our data show that digoxin-furosemide pretreatment significantly reduced serum potassium from 4.39 to 3.75 mEq/L in dogs on normal diets. In a recent study we observed smaller serum potassium reduction (4.48 to 4.10 mEq/L) in dogs pretreated with only furosemide for the same period.[1] Since increased severity of hypokalemia is frequently associated with increased instability of the cardiovascular system, the results of the present study were not entirely expected.

Dogs pretreated with digoxin and furosemide showed increased cardiac output as the result of increased heart rate and stroke volume in response to KCl infusion. This was observed when the serum potassium concentrations reached 5.5 mEq/L, but similar levels in serum potassium were not associated with increased cardiac output in untreated animals. In the absence of digitalis, increased cardiac output has been reported at serum potassium concentrations of 6.9 to 9.1 mEq/L.[1,4] The pharmacological actions of digitalis may provide a possible explanation for the increased positive inotropic effect of potassium observed in this study. Cardiac glycosides, for example, inhibit

sodium/potassium stimulated membrane ATPase.[5,6] Further depletion of cellular potassium is therefore possible through this action of digitalis, in addition to the furosemide-induced hypokalemia. An increase in serum potassium concentration from potassium infusion can, however, stimulate the sodium/potassium pump[7] and thereby oppose the digitalis inhibition of the sodium/potassium pump, thus favoring intracellular potassium restoration. An increase in extracellular potassium will also favor the concentration gradient for transmembrane movement of potassium ions into the cell. Repletion of lost intracellular potassium should improve the disturbed electrophysiology as well as the contractility of the myocardium. Sack et al[8] have shown a reduction in contractility of papillary muscles in potassium-depleted cats. Their data suggest that chronic potassium deficiency reduces the calcium binding of the myocardial sarcoplasmic reticulum, thus compromising the excitation-contraction coupling system essential for contractility. It is known clinically that hypokalemia not only enhances digitalis dysrhythmias but also antagonizes the cardiotonic effect of the glycosides. Cardiac dysrhythmias in hypokalemic digitalized patients and in hypokalemic nondigitalized patients have been effectively treated with careful infusion of potassium chloride.[9,10]

Dogs pretreated only with furosemide showed an increased incidence of cardiac dysrhythmias during infusion with nonlethal doses of KCl, and all succumbed during 3.2 mEq/kg KCl infusion.[1] However, 3 out of the 6 digoxin-furosemide pretreated dogs in the present study survived infusion of 3.2 mEq/kg KCl. The rate of change and the concentration of extracellular potassium can profoundly influence the cardiac electrophysiology. A rapid increase in serum $[K]^+$ in hypokalemic dogs shortens duration of the action potential and depresses the rate of diastolic depolarization, thus suppressing spontaneous pacemaker activity.[4] Emergence of potential pacemakers and abnormal conduction pathways could then prevail. Further increases in extracellular potassium can suppress diastolic depolarization to the point of cardiac asystole. Survivors in the present experimental animals maintained significantly lower peak serum K^+ concentrations (8.0 vs 12.3 mEq/L) in comparison with the nonsurvivors during the KCl 3.2 mEq/kg/hr infusion, thus resulting in less disturbance of cardiac rhythm.

The survivors among the treated animals had excreted 15.1 mEq of K^+ at the end of the KCl infusion. Infusion of 3.2 mEq/kg KCl into a 20-kg dog represents a total dose of 64 mEq. Since 15.1 mEq K^+ were excreted in the urine during and following the infusion period, 48.9 mEq K^+ were retained in the experimental animals. A 20-kg dog has an extracellular fluid compartment of about 5 L. Assuming the retained K^+ was evenly distributed in the extracellular compartment, then serum $[K]^+$ should have been increased by about 10 mEq/L. The average serum $[K]^+$ before the KCl infusion was 3.75 mEq/L. If the total infused dose of KCl were evenly distributed in the extracellular space, the serum $[K]^+$ at the end of the infusion period should have been 13.75 mEq/L. The difference between the calculated level of 13.75 mEq/L and the observed level of 8.0 mEq/L suggests intracellular movement of K^+ ions.

Cellular uptake of potassium may be more effective in digoxin-furosemide pretreated dogs than in untreated control animals and in the furosemide-pretreated group, thus facilitating the positive inotropic response of digitalis during mild elevations of serum $[K]^+$ and possibly protecting the myocardium against otherwise lethal infusions of KCl.

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Guest Discussion

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The data presented by Dr. Kawamura and his associates are both timely and clinically relevant. During the past 24 months, I have personally been involved in 4 panel discussions, portions of which were concerned with the anesthetic implications of preoperative hypokalemia, the additive interactions of hypokalemia and digitalization, and the need for guidelines upon which to base IV potassium administration in these situations. In each of these instances I, like other panelists, had to rely on speculation since there have been minimal data available describing the potential anesthetic effects of potassium depletion and the acute IV administration of potassium to the anesthetized patient.

In clinical practice, it is the potential for serious cardiac dysrhythmias which are of concern in caring for hypokalemic patients, particularly if they are digitalized. There are abundant data to support the conclusion that both hypokalemia and digitalis have the potential for inducing significant alterations in cardiac rhythm. Electrophysiologically, each of these factors is known to enhance diastolic, or phase-4, depolarization in the automatic (pacemaker) cells of the heart and by competitive pacemaker interaction to produce serious, perhaps even life-threatening arrhythmias. In the anesthetized patient, relative hypoxia, hypercarbia, acidosis, acute cardiac dilitation, and certain surgical manipulations additionally tend to accentuate arrhythmias produced by this mechanism.[1]

There are also abundant data to support the conclusion that restoration of a relatively more physiologic transmembrane ionic balance by increasing extracellular potassium will frequently suppress arrhythmias due to pacemaker interaction. Electrophysiologically, a relative increase in extracellular potassium is known to decrease the rate of diastolic, or phase-4, depolarization of automatic cardiac cells, to reduce automaticity, and to decrease the potential for arrhythmias.

When it becomes necessary to administer IV potassium in the anesthetized patient, the key question is, at what rate can it be utilized safely? The data presented by Dr. Kawamura and associates can be, in part, directed to this question.

In their studies, animals were rendered hypokalemic by furosemide and digitalized to a therapeutic level. Each animal was then anesthetized with a common clinical combination. Under these circumstances, the IV infusion of 1.6 mEq/kg of KCl for 60 minutes produced a peak serum potassium concentration of about 7 mEq/L. Similarly, in the 3 animals which survived the IV infusion of 3.2 mEq/kg for a similar period of time, a peak serum potassium concentration of 8 mEq/L was measured. In other words, serum potassium concentrations of 7 and 8 mEq/L were well tolerated by dogs *anesthetized* with thiopental, N_2O-O_2-halothane. Surawicz and associates,[2] studying the effects of various rates of potassium infusion in awake patients, determined "that a temporary increase of plasma potassium concentration to a level of 7.0 to 8.0 mEq/L carried no risk of ventricular standstill, ventricular fibrillation, or a significant depression of contractility."

When taken together, the data of Dr. Kawamura obtained in anesthetized animals and those of Surawicz obtained in awake patients suggest a reference level which can be used in administering potassium to patients. As long as *temporary* peak serum potassium values of 7 to 8 mEq/L are not exceeded, there should be minimal deleterious hemodynamic consequences. This portion of Dr. Kawamura's data is quite important new information.

I thank the University of Utah group for presenting this interesting information to us and encourage their continuing interest in this and related problems of ionic imbalance in patients presented for anesthesia and surgery.

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Clinical Reports

Endotracheal Tube Cuff Herniation: A Cause of Delayed Airway Obstruction

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AIRWAY obstruction, secondary to endotracheal tube cuff malfunction, was reported[1] shortly after cuffed tubes were introduced and has been reviewed[2] in detail elsewhere. We present a case of probable cuff occlusion of a mainstem bronchus which is unusual in that the occlusion manifested itself after an hour of anesthesia, during which the airway had been adequate and the position of the endotracheal tube had remained unchanged.

THE CASE

The patient was a 28-year-old male who had suffered massive maxillofacial trauma 5 days prior to admission and who was now scheduled for application of arch bars, tracheostomy, and internal fixation of multiple fractures. On physical examination the patient had moderately severe cervical and facial swelling and could not open his mouth more than 2 cm because of pain. The remainder of the examination, laboratory data and chest X-ray were normal. Meperidine 100 mg, diazepam 10 mg, and atropine sulfate 0.6 mg were administered intramuscularly 90 minutes prior to induction of anesthesia. On arrival in the operating room, an IV infusion was started and a blood pressure cuff, a precordial stethoscope, and ECG electrodes were applied. A blind nasal intubation was planned, and both nostrils were sprayed with 4 percent lidocaine and 0.125 percent phenylephrine. The largest Endotrol§ endotracheal tube that would easily pass the nasopharynx was 6 mm in internal diameter. During further passage of the tube beyond the nasopharynx, difficulty in advancement was encountered when good breath sounds were heard through the tube. The entire tube was therefore rotated 180° and easily advanced several cm into the trachea. After the cuff was inflated to a "just seal" volume (25 cc), bilateral breath sounds were heard and the tube secured in position. Anesthesia was then induced with thiopental and maintained with meperidine and N_2O 65 percent in O_2. Following positioning for tracheostomy and after reconfirming bilateral ventilation, the patient was allowed to breathe spontaneously with an occasional assisted breath. The operation proceeded uneventfully for 1 hour, at which time the patient's airway appeared to become partially obstructed, with diminished excursion of the rebreathing bag and questionably asymmetrical expansion of the chest. Positive pressure respiration was difficult, although the patient's color remained

§Endotrol®—endotracheal tube with high-volume cuff and controllable tip. National Catheter Corporation, Argyle, New York.

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good. Withdrawal of the tube 2 cm was minimally corrective, but partial deflation of the cuff immediately eliminated the difficulty. Shortly thereafter, tracheostomy was performed and positive pressure ventilation begun. The remainder of the procedure was uneventful. A chest roentgenogram in the recovery room showed patchy left upper lobe atelectasis and total left lower lobe collapse, which cleared with physical therapy and coughing.

DISCUSSION

In an attempt to define a possible mechanism for this episode of late airway obstruction, the endotracheal tube cuff was reinflated with 20 cc of air, demonstrating an unusual configuration (fig 1). The location of the cuff herniation, coupled with left upper lobe atelectasis and left lower lobe collapse, led us to believe that the tip of the tube had been near the carina, perhaps partially endobronchial, and the original cuff volume had been slowly expanding due to the effect of N_2O.[3] This expansion, when combined with the effect on the cuff of its being warmed to body temperature, allowed the cuff to herniate into the left mainstem bronchus after 1 hour of anesthesia. At this point the patient may well have had a total collapse of the left lung, which we were only partially able to expand with positive pressure respiration over the next 4 hours of anesthesia.

To test the hypothesis of cuff malfunction, we constructed a plastic tracheal-mainstem bronchi model, placed the tip of an Endotrol tube into the right mainstem bronchus with the cuff just superior to the carina, overinflated the cuff slightly with 30 cc of air (pressure = 50 torr) and placed the model in a 37° C water bath for 45 minutes. At the termination of this period, the cuff had developed a similar deformation (fig 2), filling the entire "left mainstem" of the model. An attempt to duplicate this experi-



FIG 1. Endotrol endotracheal tube cuff after removal from the patient and inflation with 20 cc of air. The cuff is oriented as it was in the patient. (Viewer's right side is the patient's left side.) Note herniation of the cuff on the patient's left side.



FIG 2. Endotrol endotracheal tube after removal from tracheal-mainstem bronchi model. Orientation as in fig 1. Note herniation of the cuff on the model's left side.

ment with a Portex* disposable tube was unsuccessful because the cuff would not distend to fill the model bronchi.

We present this case to draw attention to the fact that stretching of an endotracheal tube cuff can occur *in vivo* with certain high-volume cuffed tubes, especially if exposed to N_2O. This may cause the cuff to slowly remodel itself to conform to the anatomy, thus causing partial airway obstruction some time after tube position has been confirmed and stabilized. We suggest an examination of cuff configuration after removal in any case of unusual airway obstruction as a possible source of information concerning the mechanism of obstruction.

*Portex®—endotracheal tube with high-volume cuff. Smith Industries, Inc., Industrial Way, Wilmington, Massachusetts.

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Potency of Metocurine During Halothane-N_2O and N_2O-Narcotic Anesthesia

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A CLEARLY defined relative potency for a neuromuscular blocker is necessary for clinical administration and comparison with other muscle relaxants. Prior studies on metocurine (dimethyltubocurarine, Metubine®) report a variety of potencies for metocurine under a wide array of experimental conditions.[1-4] This report describes metocurine dose-response curves in 6 patients anesthetized with halothane-N_2O anesthesia and in 6 patients receiving N_2O-narcotic anesthesia.

METHODS

All studies were performed during elective surgery on ASA Class I to III patients. The weight range was 44 to 81 kg (63.4 ± 3.5 kg, mean ± SE). The age range was 36 to 77 years (61.8 ± 3.9 years). Preanesthetic medication was with meperidine 1 mg/kg and atropine 0.4 mg IM. Two patients receiving N_2O-narcotic anesthesia were premedicated with morphine 0.15 mg/kg. Anesthetic induction and tracheal intubation were performed with thiopental. Six patients were anesthetized with halothane (end tidal concentration 0.35 ± 0.03 percent, mean ± SE) plus 60 percent N_2O in O_2. Six other patients were anesthetized with 70 percent N_2O in O_2, supplemented with IV meperidine 2.7 ± 0.14 mg/kg. Oxygen concentrations were monitored with a Harris-Lake fuel cell. Tympanic membrane temperatures were 36.6 ± 0.2° C. Mechanical ventilation produced mean $Paco_2$ = 36 ± 2 torr for the halothane-N_2O group and 30 ± 1 torr for the N_2O-narcotic group. The ulnar nerve was stimulated supramaximally at 0.2 Hz by a Model NS-2 peripheral nerve stimulator. Thumb adduction force was measured with a force-displacement transducer and recorded on a polygraph. Using the cumulative dose-response curve method,[4] metocurine was administered in 2 mg increments until at least 85 percent twitch-height depression was obtained. Twitch heights were stable prior to any metocurine dose. Log dose-response curves were calculated using regression analysis. Doses resulting in 30, 50, and 80 percent block were determined from the curves. Slopes of the dose-response curves were compared by analysis of covariance.

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TABLE

Mean ± SE Metocurine Requirements (mg/kg) During Halothane-N_2O and N_2O-Narcotic Anesthesia in 12 Surgical Patients

Twitch-height depression	Halothane-N_2O	N_2O-narcotic
30%	0.060 ±.010	0.083 ±.010
50%	0.078 ±.010	0.105 ±.010
80%	0.116 ±.010	0.154 ±.010

RESULTS

The table shows the average Metubine requirements for 3 levels of neuromuscular block. The figure displays the composite dose-response curves. The slopes of the dose-response curves did not deviate from parallelism. No change in blood pressure or heart rate was observed with any metocurine dose.

DISCUSSION

Recently, interest in metocurine has increased because the drug appears to have few cardiovascular effects, as in this study and others.[5,6] This study reports the potency of metocurine during conditions similar to Miller's studies with d-tubocurarine and pancuronium.[7] Comparison of Miller's results with the present data during halothane-N_2O anesthesia yields a potency ratio of 2:1 for d-tubocurarine-metocurine and 1:4 for pancuronium-metocurarine. These data show metocurine is 1.3 times more potent during 0.35 percent halothane-N_2O than during N_2O-narcotic anesthesia. The metocurine requirements during N_2O-narcotic anesthesia are approximately 40 percent higher than those reported by Donlon et al.[4] Several possible reasons for this difference come to mind. First, unlike this study, Donlon's report contained no data concerning method or adequacy of ventilation. Carbon dioxide retention could account for an apparent greater potency of metocurine. Second, the patients in this study received nearly 3 times as much meperidine intravenously as did Donlon's group. Although meperidine is not considered to have significant interactions with neuromuscular blocking agents, an antagonism of metocurine could account for the difference between the 2 studies. Finally, since statistical manipulations differed between the 2 studies, the different potencies may be related to mathematical manipulations.

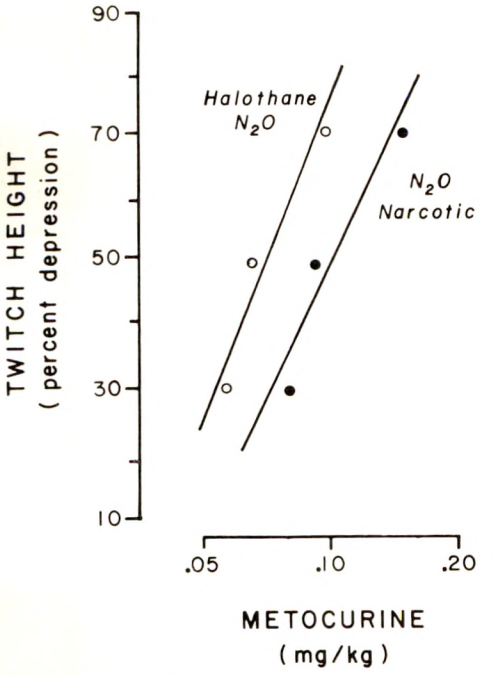


FIGURE. Twitch-height depression is plotted as a function of mean metocurine cumulative dosage for 12 surgical patients during halothane-N_2O (open circles) or N_2O-narcotic (closed circles) anesthesia.

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Internal Jugular Vein Location with the Ultrasound Doppler Blood Flow Detector

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MANY technics utilizing various anatomical landmarks have been described for location of the internal jugular vein.[1] Despite strict adherence to the described technics, the internal jugular vein may not be located when percutaneous catheterization is attempted or inadvertent carotid artery puncture may occur. Furthermore, anatomical landmarks may be difficult to define, particularly in obese, short-necked individuals or pediatric patients. We have utilized an ultrasound Doppler blood flow detector to determine transcutaneously the precise location of the internal jugular vein as it traverses the neck.

METHODS AND RESULTS

The supine awake or anesthetized patient is placed head-down with the head turned maximally to the left for location of the right internal jugular vein. Starting near the midline at the level of the thyroid cartilage, an ultrasound Doppler pencil-shaped flow detector probe is moved laterally until the characteristic pulsatile sound of blood flow in the carotid artery is audible. This area is noted with a marking pencil and the probe then moved further laterally until blood flow in the internal jugular vein is detected. The low-velocity venous flow produces a more continuous low-frequency signal that may be described as a "windstorm" or "hum." This site is also marked and the process repeated 3 to 5 cm above and below the original markings to delineate the course of the artery and vein. In our experience with adult patients the internal jugular vein is 1 to 3 cm lateral and parallel to the carotid artery. The needle or catheter is then inserted along the line corresponding to the internal jugular vein. Although we feel the pencil-shaped probe is the easiest and most reliable of the probes for this technic, we have also successfully used the flat probe designed for arterial pressure monitoring, as well.

DISCUSSION

Location of the internal jugular vein with the ultrasound Doppler blood flow detector takes the "guesswork" out of finding the vein prior to catheterization. It is essential that the head be turned maximally before locating the blood vessels. This serves to tense the skin over the vessels and, we feel, to place the internal jugular vein in a position more lateral and parallel to the carotid artery. Obviously, landmarks determined with the flow probe become meaningless should skin movement occur before attempted internal jugular vein catheterization.

We conclude that location of the internal jugular vein with an ultrasound Doppler pencil-shaped flow probe offers a practical and easily applied improvement on technics dependent on anatomical landmarks. Although we have used this approach most extensively in adults, it would seem equally applicable in younger age groups or other patients, such as the short-necked or obese individual, in whom anatomical landmarks are equivocal. Its use should increase the success rate of internal jugular vein catheterization while reducing inadvertent carotid artery puncture. Although, some readers may feel that the use of this Doppler technic is not necessary in the routine patient in the operating room, they may find it more applicable in the postsurgical patient where the anatomy of the neck may be distorted.

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Laryngospasm as an Early Indicator of Aspiration

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Unrecognized at the time of occurrence, regurgitation and aspiration of gastric contents during anesthesia can cause debilitating postoperative pulmonary atelectasis and pneumonia.[1,2] Although it has been recognized that the presence of blood, mucus, or aspirate in the pharynx can precipitate laryngospasm, the possibility that laryngospasm may be an early indicator of inapparent regurgitation and aspiration of gastric contents has not been widely emphasized. The following case report is illustrative of a number of incidents in which we have found laryngospasm to be an early sign of what would otherwise be considered silent regurgitation and aspiration.

REPORT OF A CASE

A 19-year-old man (weight 86 kg) was scheduled for removal of femoral pins from both hips under general anesthesia. Except for bilateral osteotomies for slipped capital femoral epiphyses one year earlier, the medical history, physical examination, and laboratory findings were unremarkable. Ninety minutes prior to induction of anesthesia and 10 hours after his last oral intake, the patient received Innovar® (2 ml) and atropine (0.5 mg) intramuscularly as premedication. Anesthesia was induced with thiopental (300 mg) intravenously in divided doses and maintained with halothane (0 to 2.5 percent), N_2O (66 percent), and O_2 by mask. Shortly after induction, an oropharyngeal airway was inserted, and ventilation was easily assisted. Approximately 15 minutes later, the patient's lower extremities were elevated 45° from his trunk, and the operating table was tilted 15° head down to facilitate surgical cleansing and approach.

Five minutes after the surgical preparation of both hips had begun, the patient developed signs of laryngospasm: inspiratory stridor, retraction of the suprasternal notch, decreased compliance, and subsequent lack of breath sounds. After an unsuccessful attempt to overcome the laryngospasm with positive airway pressure, succinylcholine (20 mg) was given intravenously to facilitate controlled ventilation. Because inspection of the pharynx was unremarkable, it was concluded that the laryngospasm was a result of light anesthesia; therefore, thiopental (100 mg) was given intravenously, and halothane (1.5 percent), N_2O (66 percent), and O_2 were continued by mask. Five minutes after assisted ventilation had been restored, the patient again developed laryngospasm even though the depth of anesthesia was judged to be adequate. Succinylcholine (20 mg) was administered, and the pharynx was inspected using a laryngoscope; again the pharynx was found to be free of secretions. Laryngospasm occurred a 3rd time approximately 10 minutes after the legs had been lowered and the surgical incision had been made. At this time succinylcholine (80 mg) was given, and the trachea was intubated with a cuffed endotracheal tube. During the laryngoscopy and intubation, no secretions were noted in the pharynx or trachea. Breath sounds were bilaterally equal and normal. Fifteen minutes later, the anesthesiologist noted that the respiratory rate had increased from 18 to 32 breaths per minute and that the blood appeared slightly dark. An arterial blood gas determination during assisted ventilation with 33 percent O_2 showed pH 7.30, P_{CO_2} 42 torr, P_{O_2} 68 torr, and base deficit 6. After the position of the endotracheal tube was checked, the chest auscultated, and the inspired O_2 concentration increased to 50 percent, the arterial blood gas determination showed pH 7.30, P_{CO_2} 38 torr, P_{O_2} 75 torr, and base deficit 7. Sodium bicarbonate (50 mEq) was given.

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At the conclusion of surgery, the trachea was extubated as the patient regained consciousness. In the recovery room, auscultation of the chest revealed rhonchi over the posterior aspect of the right lung field. Comparison of the preoperative chest roentgenogram with one obtained in the recovery room revealed a new opacity in the right upper and middle lobes which was consistent with aspiration pneumonitis. Arterial blood gases while the patient breathed 60 percent O_2 via mask were pH 7.37, P_{CO_2} 43 torr, P_{O_2} 86 torr, and base deficit 1. After treatment for 24 hours with physical therapy, humidified O_2, and Bronchosol via IPPB, the physical and roentgenographic findings were markedly improved. The rest of the hospital course was unremarkable.

DISCUSSION

Regurgitation and subsequent aspiration of gastric contents during anesthesia are usually readily identified phenomena; consequently, immediate therapy can be instituted to minimize pulmonary damage. However, in some situations regurgitation and aspiration occur and are not recognized until a serious pulmonary problem develops postoperatively.[1,2] Silent or unrecognized regurgitation of gastric contents has been reported to occur in 4 to 26.3 percent of all patients receiving general anesthesia; and in up to 76 percent of this group, tracheal aspiration accompanied regurgitation.[3-6] Although anesthetic technics that might have predisposed to these complications were used in many of the earlier studies, a recent study employing newer anesthetic practices also found a comparable regurgitation incidence of 14.5 percent.[7] The factors that these studies suggest predispose to the high incidence of regurgitation and aspiration include gastric distention, increased intragastric pressure, airway obstruction, stormy induction or maintenance of anesthesia, the Trendelenburg, lateral, or lithotomy positions, certain anesthetic agents, uncuffed endotracheal tubes, abdominal operations, poor postoperative care, and inexperienced personnel.

The case presented here is representative of several such incidents in which we have found inapparent regurgitation and aspiration to be associated with laryngospasm during anesthesia. Although this frequent complication of inhalational anesthesia has been associated with slow inductions, light levels of anesthesia, rapid administration of irritant inhalational agents, painful or mechanical stimulation, airway obstruction, and liquid material in the pharynx, laryngospasm has not commonly been associated with inapparent aspiration. Because in this case the episodes of laryngospasm did not appear to be related to other possible causes of laryngospasm, mechanical stimulation of the pharynx and larynx by secretions was suspected. However, direct visualization of the larynx did not confirm this suspicion; and, therefore, measures were not taken to isolate the trachea from the pharynx. Since it has been estimated that at least 25 ml of aspirate with a pH less than 2.5 is required to produce pneumonitis,[8] it would appear that regurgitation and aspiration of small amounts of liquid occurred prior to each occurrence of laryngospasm. Presumably, such small amounts of liquid could be distributed quickly in the tracheobronchial tree and, thereby, not be detected on inspection of the pharynx. In the case discussed here, the initiating cause of this series of regurgitations and aspirations may have been the positioning of the patient prior to the surgical cleansing. Although this patient did not have abdominal distention, such positioning of patients with distended abdomens has been shown to increase intragastric pressure. Therefore, other considerations aside, it may be advisable to insert an endotracheal tube in similar situations even though the unfavorable position is to be maintained only for a short period.

In summary, the case reported here is representative of a number of incidences in which laryngospasm was found to be a sign of inapparent regurgitation and aspiration. Although it would seem that the terms silent regurgitation and aspiration, as initially defined, cannot be used to describe the reported case, we have found that many cases of so-called postoperative silent aspiration are in fact characterized by intraoperative laryngospasm. Therefore, we believe that by being cognizant of this association one can more quickly identify and treat inapparent regurgitation and aspiration prior to the development of severe postoperative morbidity.

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Arterial Blood Gases in Mothers and Infants During Ketamine Anesthesia for Vaginal Delivery

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SEVERAL previous studies have reported on the use of ketamine for anesthesia in both vaginal delivery and cesarean section.[1-4] Except for reports of unpleasant dreams, doses of less than 2 mg/kg/IV have generally been found safe for the mother and infant.[1,3] Doses above 2 mg/kg/IV have been associated with some incidence of neonatal depression.[2] Doses of 0.25 to 0.50 mg/kg/IV are now often used for vaginal delivery.[3]

Most studies on the use of ketamine, however, have not looked closely at arterial blood gas studies in mothers and infants. Akamatsu, for example, while reporting an extensive series utilizing doses of 12.5 to 25.0 mg of ketamine with good fetal outcome as measured by Apgar scores, failed to report arterial blood gas data. An exception is the report by Galbert who, utilizing 2 mg/kg/IV or less prior to delivery, reported blood gas and acid-base values which were interpreted as normal for the clinical conditions.[4] At a time when the mother was breathing 100 percent O_2 delivered at 61/min by face mask, Pao_2 was 306 ± 66.74 torr. Zsigmond et al, on the other hand, recently reported arterial hypoxemia in nonpregnant females receiving 2 mg/kg/IV while breathing room air.[5] Some of the patients in the series reported by Zsigmond received additional drugs prior to administration of ketamine, but the authors appeared to feel this was not responsible for the hypoxemia.

In our institution it has been the policy to use low-dose ketamine (0.25 to 1 mg/kg/IV) in selected cases for vaginal delivery, with mothers often breathing room air. Because of the study of Zsigmond and the paucity of blood gas studies in other reported clinical studies, we decided to look at these parameters.

MATERIAL AND METHODS

Ten ASA IE mothers who presented with vertex presentation ready for delivery and with no medication for labor were given slowly, in a single injection, 1 mg/kg/IV ketamine for vaginal delivery. All were breathing room air. None required airway management or vomited. Additional medication was not required for delivery in this group. Maternal arterial blood gases in heparinized glass syringes were obtained at the time of delivery or 3 minutes after administration of the drug, whichever came

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first. All mothers delivered within 5 minutes of the administration of the drug. Apgar scores were determined on the infants at 1 and 5 minutes. At delivery the cord was immediately double clamped and samples of umbilical venous blood taken in heparinized glass syringes for blood gas analysis.

Controls were 10 ASA IE mothers who received no more than 50 mg of meperidine for labor and were delivered vaginally with spinal anesthesia. Mothers were excluded from this group if there was electrocardiographic evidence of fetal distress during labor. Arterial blood gas samples were drawn from the mother and umbilical venous samples from the infant at delivery while the mother was breathing room air. Apgar scores were done at 1 and 5 minutes. All mothers were hemodynamically stable due to intravenous infusion of large volumes of lactated Ringer's solution prior to the spinal anesthesia and left uterine displacement subsequent to the spinal but prior to delivery.

RESULTS

There were no statistically significant differences between the ketamine group (fetal and maternal) and our 10 control mothers and infants (see table). One mother in the ketamine group had a Pao_2 of 80 torr. No cause for this was apparent. She had neither visible obstruction to the airway nor hypoventilation, although she was obese, which may have contributed to the hypoxemia. Her infant had normal Apgar scores and acid-base values.

The infants in both groups had good Apgar scores (8 or over at 1 minute). There was no evidence of hypertonia or other difficulties with these infants.

All mothers receiving ketamine exhibited elevation of blood pressure and pulse but this was not severe in any case. Two of the 10 mothers receiving ketamine seemed restless after delivery. They were successfully managed with 10 mg of diazepam slowly injected intravenously after arterial blood samples had been obtained. None of the mothers at a subsequent interview complained of unpleasant subjective experiences during anesthesia and delivery.

TABLE
Blood Gas Values and pH*
(Room Air ± SD)

		Ketamine group	Controls	t-test
Pao_2	ma†	96.94 ± 6.97	99.58 ± 3.35	1.079
$Paco_2$	ma	30.60 ± 4.48	32.35 ± 4.20	0.901
pH	ma	7.445 ± 0.066	7.433 ± 0.058	0.427
Po_2	uv‡	32.01 ± 3.19	32.46 ± 2.34	0.359
Pco_2	uv	34.91 ± 3.66	36.16 ± 3.52	0.777
pH	uv	7.356 ± 0.058	7.337 ± 0.042	0.829

*Room air ± SD
†Maternal arterial samples
‡Fetal umbilical venous samples

DISCUSSION

The use of ketamine in obstetrics has been widely reported. The article by Zsigmond et al caused the present authors to examine the literature and the use of the compound on their clinical service more closely. Only the article by Galbert contained exhaustive blood gas studies; these, however, were obtained at a time when the mothers were breathing 100 percent O_2 by face mask 61 flow, and the resulting maternal mean Pao_2 of 306.60 ± 66.74 was not reassuring. Higher arterial O_2 tensions might have been expected in these young hyperventilating mothers ($Paco_2$ = 28.20 ± 6.04) when inhaling 100 percent O_2 if ketamine had no effect on O_2 exchange.

We are not sure why patients reported by Zsigmond et al exhibited such profound hypoxemia.[5] The dose of ketamine was not excessive. We did not find hypoxemia when ketamine was given slowly in a dose of 1 mg/kg/IV. Our recommendation would be to give ketamine slowly in a dose of 0.25 to 1 mg/kg/IV for vaginal delivery. We often give O_2 by face mask but it did not appear from our study to be necessary in normal mothers, although all patients must be closely observed for possible airway obstruction or vomiting. We avoid the use of ketamine with hypertension associated with pregnancy.

In summary, although ketamine has been widely used for vaginal delivery and cesarean section in doses of 0.25 to 2 mg/kg/IV, arterial blood gas studies have not been widely reported, particularly with mothers breathing room air during delivery performed under ketamine anesthesia. After a recent report that revealed serious hypoxemia when ketamine was used in nonpregnant females, we investigated this possibility in mothers receiving ketamine in doses of 1

mg/kg/IV for vaginal delivery. We found no difference between controls and the ketamine group in either mothers or infants with regard to pH, P_{CO_2}, P_{O_2}, and Apgar scores.

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Lymph Leakage Following Catheterization of the Right Subclavian Vein

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THE subclavian vein may be used as the site for insertion of an endocardial pacing wire,[1,2] particularly in children, in whom suitable peripheral veins can be difficult to find. A case of lymph leakage around a pacemaker catheter following insertion into the right subclavian vein is described below.

CASE REPORT

A 6-year-old boy developed atrioventricular dissociation during total correction of tetralogy of Fallot, which required insertion of a pacemaker using temporary epicardial electrodes. His progress was satisfactory until the 26th postoperative day, when function of the pacemaker became erratic, with a sudden increase in threshold. It was decided to put in an endocardial pacing electrode while awaiting delivery of a suitable pediatric lithium-cell pacemaker.

The child was anesthetized and, using an aseptic technic, the right subclavian vein was punctured at the midclavicular point on the first attempt with a 16-gauge cannula. A free flow of venous blood was obtained and a No. 4 Fr. bipolar pacing electrode was easily passed along the cannula and positioned in the right ventricle. The entire procedure was uneventful.

Two days later milky fluid, confirmed as lymph by laboratory examination, began to leak out onto the skin around the subclavian catheter. Treatment was conservative in the absence of a chylothorax. Lymph drainage abruptly stopped 4 days later, when manipulation of the endocardial wire was required. On the 56th postoperative day the child had a permanent lithium-cell pacemaker implanted. Removal of the subclavian endocardial electrode was uneventful and there was no recurrence of lymph drainage.

Preoperative angiograms revealed a normal left-sided aortic arch with a right-sided innominate artery, implying that the arrangement of the great veins was normal and that the thoracic duct was situated normally on the left side.

DISCUSSION

Cannulation of the right subclavian vein is often chosen in preference to the left because of ease of access for the right-handed operator, because the right-sided vein is straighter than the left, thereby facilitating cannulation, and, finally, because use of the right subclavian vein avoids the potential risk of damage to the thoracic duct.[3] Moosman[4] reviewed the anatomy of the subclavian vein and recommended venipuncture near the junction of the axillary-subclavian veins, where there is less risk of damage to nerves and to the subclavian artery because of the interposition of the

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FIGURE. The anatomical relationships of the right lymphatic duct (marked with pointer) to the subclavian vein, internal jugular vein, and anterior scalene muscle.

anterior scalene muscle (see figure). The right lymphatic duct crosses the anterior scalene muscle to enter the superior margin of the subclavian vein near its junction with the internal jugular. Placement of a needle above or behind the vein or, alternatively, penetration of both walls could injure the right lymphatic duct.

A wide variety of complications associated with subclavian catheterization has been reported.[3,5] However, although damage to the lymphatic system is recognized as a potential risk, only one other case has been recorded. Vellani, et al,[6] reported injury to the thoracic duct in a patient following insertion of an endocardial pacing catheter by entering the left subclavian vein a 2nd time. The lymph drainage stopped spontaneously after 4 days.

In our case, despite care in choosing the lateral position of the right subclavian vein and despite the ease of venipuncture as well as the absence of difficulty in inserting the pacing wire, damage to the right lymphatic duct probably occurred at the time of insertion. In view of the anatomical relationship of the right lymphatic duct to the subclavian vein, it is difficult to imagine how the damage occurred unless the right lymphatic duct was abnormally situated, a possible feature in a child with multiple congenital abnormalities.

At the time of remanipulation of the electrode catheter there was a small gush of blood on first disturbing the catheter, and thereafter all lymph drainage ceased. If the right lymphatic duct joined the subclavian vein just proximal to the point of puncture, it is possible that the pacing catheter in situ may have established a track along which free drainage from the lymphatic duct could occur to the exterior.

SUMMARY

Leakage of lymph following puncture of the right subclavian vein occurred in a patient, requiring a pacemaker catheter. The lymph drainage settled spontaneously after 4 days on remanipulation of the pacing wire.

ACKNOWLEDGMENTS

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Epidural Anesthesia for Cesarean Section in Kyphoscoliosis

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ANESTHETIC management for cesarean section in a patient with severe kyphoscoliosis was successfully accomplished using a continuous lumbar epidural technic. A review of the literature has failed to reveal a prior report of this form of anesthesia for cesarean section in a patient with disease of this severity.

REPORT OF A CASE

A 25-year-old woman with severe idiopathic kyphoscoliosis was admitted to the obstetrical ward during her 36th week of pregnancy complaining of progressively increasing dyspnea. At age 21 the patient delivered a 3.3 kg infant without anesthesia after a moderately prolonged labor uncomplicated by respiratory difficulty.

Throughout the present pregnancy the patient had been able to perform housework, climb stairs, and ride a bicycle with only minimal discomfort. Two weeks prior to admission she noted onset of orthopnea and paroxysmal nocturnal dyspnea. Thereafter she noted increasingly severe orthopnea and progressing edema of her hands and feet. She gained 3.3 kg in the week before her admission.

Examination revealed a mildly cyanotic woman 142 cm tall weighing 54.5 kg, with a pulse of 120/min, a blood pressure of 140/90 torr, and a respiratory rate of 34/min. She had moderately severe thoracic kyphoscoliosis.

Admission chest roentgenogram showed a marked narrowing of the upper thorax and an exaggerated thoracolumbar lordosis. The cardiac size and vascularity were normal. An ECG showed sinus tachycardia, right axis deviation, and clockwise rotation of the heart. The admission hemoglobin was 11.4 gm percent. Arterial blood gases while breathing room air showed a pH of 7.36, a Pao_2 of 55 torr, a $Paco_2$ of 53 torr, and an O_2-hemoglobin saturation of 87 percent.

After admission to the obstetrical ward, the patient was given O_2 by face mask and placed at bed rest sitting up. Marked improvement was noted in her clinical condition within 48 hours, by which time the O_2 mask was replaced by nasal cannulae with a long O_2 delivery tubing to allow gradually increasing ambulation and maximal freedom of movement.

Several determinations of pulmonary function revealed an initial very low vital capacity with some improvement over the next few days. Upon admission, vital capacity and forced vital capacity were both 0.61 litre with an FEV_1/FVC of 71 percent. On the 8th day vital capacity was 0.79 litre, forced vital capacity 0.70 litre, and the

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FEV_1/FVC 75 percent. Her "predicted" vital capacity (based on height and weight) was 2.81 litre. X-ray pelvimetry suggested that vaginal delivery might not be feasible.

On the 16th day after admission, the patient went into labor following a negative oxytocin challenge test. The obstetrician decided to perform a cesarean section after 6 hours of labor when progress toward delivery stopped in spite of 2 hours of vigorous uterine contractions.

Good rapport had been established and the patient was cooperative. The surgeon was willing to operate with the patient in a semi-sitting position. We therefore elected to use epidural anesthesia. A radial arterial cannula was inserted for intermittent blood gas determinations and for continuous monitoring of arterial blood pressure. An epidural catheter was inserted into the L_3 to L_4 interspace with relative ease. Ten ml of 2 percent chloroprocaine were injected through the catheter with the patient sitting. This produced a sensory blockade to the 10th thoracic dermatome. No respiratory discomfort was noted. A drop in systolic blood pressure from 120 to 80 torr was corrected by administration of 6 mg of ephedrine and by left uterine displacement. Twelve ml of 2 percent lidocaine with epinephrine 1:200,000 were then injected through the epidural catheter and surgical anesthesia was achieved to the 8th thoracic dermatome without alteration in vital signs. Thirteen minutes after this injection, a 3.25 kg male infant was delivered through a transverse lower abdominal incision. The infant had 1- and 5-minute Apgar scores of 9 and 10, respectively. A dramatic fall in maternal blood pressure to 60 torr systolic and 40 torr mean occurred approximately 3 minutes after delivery. Her blood pressure quickly improved with administration of ephedrine, increased intravenous fluids, and lowering of the patient into a more nearly supine position. A tubal ligation and closure of the incision were performed after injection of an additional 12 ml of 3 percent chloroprocaine through the epidural catheter.

A combination of epidural bupivacaine injections and intravenous morphine provided postoperative analgesia. Twenty-six hours postoperatively, while she continued to receive nasal oxygen, arterial blood gases showed the patient to be hypercarbic and acidotic (see table). Twelve hours prior to this determination, O_2 flow had been increased; and 1 hour prior to this determination she had been given 4 mg of morphine sulfate intravenously. Her blood gases subsequently improved after O_2 flow was decreased. She was discharged from the inten-

TABLE

Serial Blood Gas Determinations

Day	O_2 Therapy	pH	P_{CO_2} (torr)	P_{O_2} (torr)	Comments
1	Room air	7.36	53	55	Admission
1	5 l/min, mask	7.33	55	291	
2	2 l/min, nasal prongs	7.23	60	135	
2	0.5 l/min, nasal prongs	7.33	55	95	
16	0.5 l/min, nasal prongs	7.39	48	89	Before labor
17	1.5 l/min, nasal prongs	7.37	53	65	Active labor
17	2 l/min, nasal prongs	7.23	50	112	10 min before delivery
17	2 l/min, nasal prongs	7.23	48	101	10 min after delivery
17	2 l/min, nasal prongs	7.37	51	81	1 hr after delivery
17	2 l/min, nasal prongs	7.40	50	107	14 hrs after delivery
18	8 l/min, mask	7.29	67	204	26 hrs after delivery
18	2 l/min, mask	7.41	49	97	After transfusion of 2 units of packed cells
22	Room air	7.47	47	63	O_2 therapy stopped
70	Room air	7.37	48	64	8 weeks postpartum

sive care unit on the 2nd postpartum day but was maintained on low-flow nasal O_2 for 3 more days. On the 8th postpartum day she and her child were discharged from the hospital.

The patient was seen in the clinic 8 weeks postoperatively. Her exercise tolerance was again good and she was able to ride a bicycle for up to several hours. Arterial blood gases while breathing room air showed a pH of 7.37, a $Paco_2$ of 48, and a Pao_2 of 64. Her vital capacity was 0.75 litre, forced vital capacity 0.71 litre, and FEV_1/FVC 81 percent.

DISCUSSION

Kyphoscoliosis, found in about 1 percent of the population of the United States, may be associated with both obstetrical and anesthetic problems during pregnancy. Lesions of the lower spine may cause changes in the pelvic architecture severe enough to lead to dystocia during labor. Lesions of the upper spine, on the other hand, may result in disorders of normal cardiac and respiratory function.[1]

In many forms of cardiorespiratory disease, further decompensation may not occur after the 6th or 7th month of pregnancy because the normal increase in maternal cardiac output reaches a plateau.[2] In kyphoscoliosis, however, the enlarging uterus encroaches progressively upon a nondistensible thorax. This encroachment occurs during a period when maternal alveolar ventilation normally continues to increase.[3] Thus the kyphoscoliotic mother is at ever-increasing risk as the pregnancy continues, and she may suffer cardiac decompensation during labor, especially if dystocia occurs. Women patients such as this one, with a vital capacity of less than 1000 ml, are particularly likely to go into heart failure, including possible maternal death.[4]

At the time of admission this patient appeared to be suffering impending respiratory failure with possible cor pulmonale. The extent of her respiratory embarrassment at that time can be appreciated by the fact that her $Paco_2$s were in the range of 53 to 60 torr. During late pregnancy the maternal $Paco_2$ is normally reduced to 32 to 33 torr,[5] with a compensatory decrease in bicarbonate so that the pH remains normal. Our patient's near normal pH suggests a chronic adaptation to a remarkably elevated $Paco_2$. It would have been interesting to have known the infant's blood gases in light of the maternal acid-base derangement, but no determination was made. The initial hemoglobin concentration of 11.4 gm percent undoubtedly further accentuated the patient's respiratory failure because of her decreased ability to transport O_2.

The patient appeared to demonstrate hypoxia-dependent ventilatory drive characteristic of chronic respiratory failure. Soon after admission and again after delivery, administration of a high concentration of O_2 was temporally associated with hypercarbia and acidemia. However, patient fatigue was present after admission, and a narcotic had been administered in the period after delivery, both of which probably also contributed to her ventilatory decompensation.

After her condition stabilized with conservative therapy, our next consideration was the management of her labor and delivery. Several series of patients similar to ours have been reported.[6-8] The authors of these reports usually advised against use of respiratory depressants such as narcotics during labor. For this reason we planned to use a continuous epidural technic for labor as well as for vaginal delivery, if that proved possible. We thought that a closely monitored epidural anesthetic would offer her good analgesia during labor without respiratory depression, and that such analgesia might minimize an undesirable rise in cardiac output.

When cesarean section was indicated early in the course of our patient's labor, a number of additional considerations were added to selection of the best anesthetic technic. Vital capacity is known to be reduced following abdominal surgery, presumably because of pain-induced limitation of respiratory excursion. Epidural anesthesia during the postoperative period has been shown to attenuate this decrease and to permit more nearly undisturbed respiratory function.[9] Additionally, postoperative improvement in vital capacity might be expected because of removal of the respiratory obstruction caused by the enlarged uterus. For these reasons we thought that continuous epidural anesthesia would prove more satisfactory than general endotracheal anesthesia even though the latter might have made intra- and postoperative ventilatory support more readily achieved should acute respiratory failure develop.

Alteration in cardiovascular function may

occur with either regional or general anesthesia. Certainly, hypotension following sympathetic blockade during regional anesthesia is a well-recognized complication. However, sudden drops in blood pressure during general anesthesia have also been described in kyphoscoliotic patients following alterations in position, presumably brought about by the distorted anatomy.[10] It is interesting to speculate on the reason for the rather sudden drop in maternal blood pressure that occurred 3 minutes after delivery (ie, 16 minutes following epidural injection). It is possible that this decline was caused by a somewhat delayed sympathetic block. However, it is also possible that this decline might have been caused by a sudden increase in venous return following the pelvic decompression of delivery, an increase in venous return which might have overloaded the right heart in the pressure of chronic cor pulmonale caused by severe kyphoscoliosis.

There is no single regimen which may be considered best for the obstetric and anesthetic management of all pregnant women with severe kyphoscoliosis. In spite of the technical difficulty that may be anticipated because of anatomic alteration, epidural anesthesia can offer a good quality of pain relief without additional respiratory embarrassment. The versatility of this technic permits its application to labor, vaginal delivery, cesarean section, and postoperative analgesia, and makes it indeed a suitable choice.

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Continuous Brachial Plexus Block for Prolonged Sympathectomy and Control of Pain

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CONTINUOUS brachial plexus block as a means of decreasing vasospasm, relieving pain, and promoting collateral circulation following upper extremity vascular accidents was suggested by Ansbro in 1946.[1] He originally described the technic using the supraclavicular approach. The longest duration of brachial block reported was less than 5 hours, and the procedure was used primarily for surgical anesthesia.

Winnie[2] in 1964 described a technic for block of the brachial plexus by a single injection through the interscalene space.[3,4] A

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continuous method using this technic was reported in 1969 by DeKrey.[5] It too was primarily used for surgical anesthesia, and the longest duration of block was 9 hours.

We have used continuous interscalene brachial plexus block in 3 patients with upper extremity vascular accidents. A radiopaque Teflon Jelco® indwelling catheter needle was used. To prevent kinking of the catheter 2 4″-by-4″ gauze sponges with a small central hole were placed over the catheter, the hub of the catheter being situated inside the hole. A plastic T-connector tubing or a plastic intravenous extension tubing was connected to the catheter to permit remote injections.[6] Free flow of local anesthetic solution was checked to note a kink in the catheter. A sterile 3-ml syringe was connected to the end of the extension tubing and taped to the skin. For extra protection a bandage was loosely wrapped around the patient's neck.

Each subsequent injection of anesthetic was preceded by an attempt to aspirate blood from the catheter to ensure that its tip was not in a blood vessel. Each injection was also followed by close monitoring of the patient for at least 30 minutes in case of an adverse response to the local anesthetic.

CASE REPORT

A 28-year-old female, with a history of drug abuse for 1½ years, accidentally injected a pulverized methylphenidate hydrochloride tablet dissolved in water intra-arterially in her antecubital fossa. There was immediate onset of pain, edema, tingling sensation, coldness, and bluish discoloration below the wrist.

A right continuous interscalene block was performed 3 hours after the accident. Bupivacaine, 30 ml of a 0.5 percent solution, produced analgesia for 5 hours along with improvement in color and 1° C elevation in temperature of the thumb and the small finger. After decompression fasciotomy, the patient was heparinized. Bupivacaine, 20 ml of 0.25 percent, was given every 6 hours.

When the catheter was removed on the 4th day there were no signs of infection, bleeding, or hematoma. The patient was able to move all her fingers with normal sensation. Good capillary refill was present. The fasciotomy wound healed well. Small areas of dry gangrene were noted on the medial aspect of the ring and long finger tips on the day of discharge. Subsequent follow-up revealed almost full recovery.

CASE REPORT

A 36-year-old male was using a jack on the day of admission when it slipped and struck his dominant right ring finger, causing a circumferential laceration of the proximal phalanx through both digital vessels.

A right continuous interscalene block resulted in 1.7° C increase in temperature with improvement in color of the distal right ring finger. Bupivacaine, 30 ml of 0.25 percent solution, provided analgesia for 4 to 5 hours. The patient was then heparinized. Analgesia was maintained with repeated injections of bupivacaine, 20 ml of 0.25 percent, every 6 hours. The catheter was removed on the 4th day. Recovery was uneventful with good capillary refill and with a 45° range of movement on the involved finger at the time of discharge.

CASE REPORT

A 28-year-old male drug addict injected a pulverized Empirin® tablet dissolved in water into a vein in his left index finger, the only vein he could find. A previous similar injection into the same vein was uneventful, but this time there was immediate onset of severe pain, edema of the whole hand with bluish discoloration of the index finger and dorsum of the hand. There was complete loss of sensation in the involved finger.

Continuous pain relief was achieved with continuous interscalene block. Bupivacaine, 20 ml of 0.5 percent, produced analgesia for 4 to 5 hours and a 1° C elevation of temperature in the left thumb and small finger. Analgesia was maintained with injections repeated through the catheter every 6 hours until the catheter was removed on the 4th day. The patient was not heparinized. The swelling subsided but the bluish discoloration of the distal left index finger persisted. Recurring pain required increasing use of narcotics. Continuous interscalene block was reinstituted 2 days after discontinuation of the 1st one. The 2nd catheter was removed 3 days after placement. Dry gangrene of the finger developed, and amputation was required 20 days after admission under regional block.

During the period of the nerve block, narcotics were not used. Diazepam 10 mg was given to relieve agitation.

SUMMARY

An anesthetic technic for long-term analgesia and sympathectomy for upper extremity vascular accident was successfully

employed in 3 patients. Narcotics were not required during this period. Neurological complications, local bleeding, and hematoma were not detected even though 2 patients were heparinized.

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Inhibition of Seizure Activity During Enflurane Anesthesia

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ENFLURANE induces EEG seizure activity in man and laboratory animals.[1,2] This activity is enhanced by low arterial P_{CO_2},[3] and appears to be directly related to the blood levels of this anesthetic. In this communication we report the paradoxical disappearance of a spiking pattern in the EEG of an epileptic patient following the administration of enflurane. Previously we made a similar observation in another patient.

CASE REPORT

A 10-year-old white male with a 6-year history of severe psychomotic seizures unsuccessfully treated with carbamazepine (Tegretol®) and diphenylhydantoin underwent elective removal of an epileptogenic focus in the left frontotemporal area.

Patient weight was 77 kg, and premedication consisted of 100 mg meperidine 90 minutes prior to onset of general anesthesia. Induction took place with fentanyl (Sublimaze®) (0.05 mg) and sodium thiopental (75 mg). Endotracheal intubation was facilitated with 40 mg succinyldicholine, and maintenance consisted of 50 percent nitrous oxide in O_2 and intermittent fentanyl. Mechanical ventilation kept P_{aCO_2} constant at 32 torr as documented by blood gas determinations.

An electrocorticogram of the affected brain area was recorded 2 hours following induction. After nitrous oxide had been discontinued for 20 minutes, the EEG showed persistent spiking activity from several leads (fig 1). Seizure activity then disappeared following 5 minutes of 4 percent enflurane inhalation. At this time the concentration of enflurane in blood was 5.41 mg percent (1 MAC = 12.8 mg percent).

After 10 minutes of 4 percent enflurane some minor seizure activity returned (fig 2) (enflurane in blood = 9.89 mg percent). The anesthetic was discontinued, and the EEG seizure activity returned to the pre-enflurane level (enflurane in blood = 3.69 mg percent).

DISCUSSION

The administration of enflurane may not be advisable in epileptics since this agent

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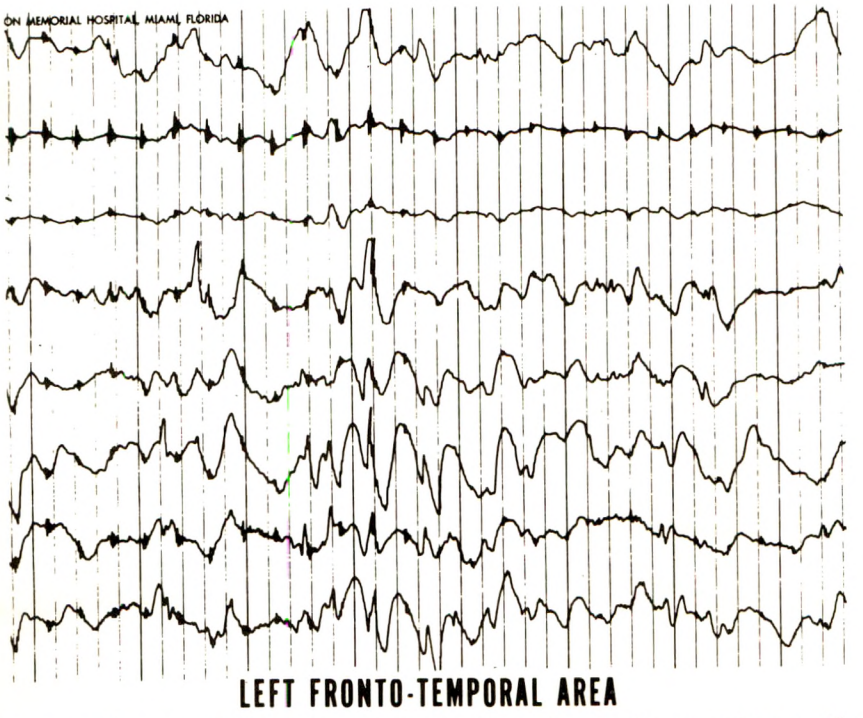


FIG 1. Electrocorticogram of left frontotemporal area before introduction of enflurane. Note spiking patterns. Fifteen-second recording.

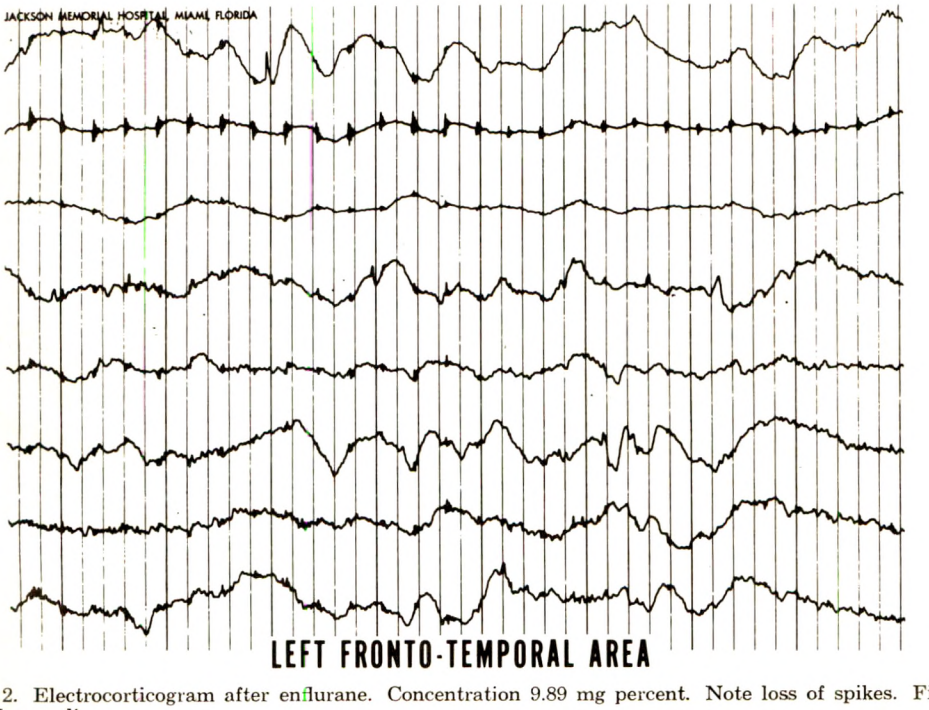


FIG 2. Electrocorticogram after enflurane. Concentration 9.89 mg percent. Note loss of spikes. Fifteen-second recording.

induces EEG seizure activity in normal patients. However, this case illustrates the depressant effect of this anesthetic on abnormal EEG pattern of an epileptic patient.

Recent animal studies[4] have indicated that thiopental may exacerbate enflurane-induced seizures. However, there are few similarities in that the patient had documented seizure both before induction of anesthesia and before the introduction of enflurane. The animals had seizures induced by enflurane and then thiopental introduced. The patient had received 1 mg/kg of sodium pentathol 2 hours before the introduction of enflurane.

While cerebral equilibration may not be reached in 5 minutes, the concentration will be rapidly approaching this because of high blood flow, and clearly enflurane introduction is the only change occurring which could affect the seizure activity. All other variables remained unchanged.

This observation suggests that enflurane-induced seizures may have a different mechanism than those seen in epilepsy; however, further clinical observations and animal investigations are necessary before enflurane's effects on epileptogenic seizure activity can be clarified.

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Curare Sensitivity in Steroid-Treated Myasthenia Gravis: A Case Report

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Sensitivity to the injection of small increments of curare has long been used as a diagnostic test in myasthenia gravis. Although anticholinesterase therapy has been the classical treatment for myasthenia gravis, steroids have been employed with increasing frequency in recent years, often allowing discontinuation of anticholinesterase drugs. However, with the exception of the report by Griggs et al[1] of an ACTH-treated patient, the response of the steroid-treated myasthenia gravis patient to nondepolarizing relaxants has been poorly documented. This report demonstrates the maintenance of curare sensitivity in a steroid-treated myasthenic patient not requiring anticholinesterase therapy.

The patient was a 51-year-old white female, 160 cm tall and weighing 87 kg, who was admitted to the University of Virginia Medical Center November 27, 1975, with a 17-hour history of left lower quadrant abdominal pain. This was unaccompanied by nausea, vomiting, or melena, and a similar episode 4 weeks previously had resolved spontaneously. A history of diverticulitis was present. Past medical history revealed multiple previous surgical procedures and allergies to morphine and hydromorphone (Dilaudid®). Her medications included isoniazid 300 mg daily; potassium chloride 20 mEq daily; and prednisone 90 mg daily. She also gave a 14-month history of generalized weakness, fatigue, and oral, extraocular, pharyngeal, and proximal muscle weakness, diagnosed in August 1975 as myasthenia gravis. The patient was initially treated with pyridostigmine 180 mg per day. In September 1975, the patient was started on prednisone 180 mg per day and, after an initial exacerbation of muscle weakness, experienced steady improvement in muscle strength. The anticholinesterase medications

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were gradually decreased and then discontinued on October 17, 1975. The prednisone was gradually decreased to 90 mg per day, and her myasthenia was felt to be in remission. On physical examination, the patient had a cushingoid appearance and a blood pressure of 130/60 torr, a pulse of 130 beats/min, a temperature of 39° C orally, and respirations of 12/min with a vital capacity of 2200 ml. Pertinent physical findings included diffuse tenderness with voluntary guarding in the left lower quadrant with no rebound tenderness. Bowel signs were present. Liver and spleen were not palpable. On neurologic examination, there was diversion strabismus, bilateral ptosis, and slight weakness of the triceps (4.5 on a scale of 5) without fatigability. Total bilirubin was 3.2 mg%, hemoglobin 13.4 g%, hematocrit 39%, serum potassium 4.4 mEq/L, and blood glucose 150 mg%. Urine showed 1+ sugar and albumin. The chest x-ray was normal, and an abdominal x-ray showed fluid levels in the ascending colon and loops of small bowel without dilatation or fluid.

The initial diagnosis was diverticulitis with perforation and the patient was treated with IV cephalothin. The temperature began to decrease, but on the day after admission severe left lower quadrant pain developed, the right lower abdominal pain increased, and the temperature increased to 38.7° C orally. Diagnoses at that time included ruptured pericolonic abscess or peptic ulcer with perforation in addition to the pre-existing diverticulitis.

The patient was brought to the operating room unpremedicated and, due to the possibility of a full stomach, an awake endotracheal intubation was performed using topical anesthesia and IV alphaprodine 30 mg for sedation. Several attempts at intubation were necessary due to a small larynx, but a 6.0-mm tube was ultimately passed and, following inflation of the cuff, induction of anesthesia was accomplished with 200 mg thiopental and anesthesia maintained with 66 percent N_2O and 33 percent O_2. Upon opening the abdomen, the abdominal relaxation was inadequate and d-tubocurarine was administered, with twitch tension in the hypothenar muscles being monitored during ulnar nerve stimulation with a Block Aid monitor. d-Tubocurarine 3 mg produced approximately a 50 percent decrease in twitch response, which was adequate for the surgical procedure. Laparotomy revealed a small pericolonic area of inflammation with no evidence of abscess or peritoneal inflammation. A right transverse colostomy was performed. At the conclusion of surgery, 50 minutes following the administration of d-tubocurarine, the patient was awake and twitch response had returned to control levels. She was taken to the intensive care unit and placed on a volume ventilator.

Approximately 2 hours postoperatively, the patient was placed on intermittent mandatory ventilation (IMV) at a rate of 12/min, at which time she had a vital capacity of 750 ml and a minute ventilation ($\dot{V}_E$) of 5 L with a rate of 17/min. After approximately 45 minutes of IMV, the patient began a trial of unassisted ventilation. After 45 minutes vital capacity was 1125 ml. inspiratory force was −30 cm of water, and arterial blood gases showed pH to be 7.44, P_{CO_2} 33.5 torr, and P_{O_2} 140 torr with an F_IO_2 of 0.4. The patient was extubated and required no further respiratory support throughout her hospital course. She was discharged on the 11th postoperative day and continued to take prednisone 80 mg daily.

Approximately 6 weeks later the patient was readmitted to the hospital for a sigmoid colectomy. At this time neurologic examination was entirely normal. Chest x-ray, ECG, and serum electrolytes all were within normal limits and blood sugar and LDH were slightly elevated. She was premedicated with diazepam, 10 mg, and atropine, 0.4 mg, IM approximately 75 minutes preoperatively. Induction of anesthesia was accomplished with incremental doses of thiopental and alphaprodine with the addition of enflurane by mask. Topical anesthesia of the larynx was achieved with lidocaine 80 mg prior to endotracheal intubation, which was accomplished without muscle relaxants. Anesthesia was maintained with 50 percent N_2O, 50 percent O_2, and 1.5 percent enflurane, and 3 mg of d-tubocurarine were again administered since twitch tension in the hypothenar muscles was observed during ulnar nerve stimulation with a Block Aid monitor. Since this failed to produce adequate abdominal relaxation, and the twitch tension had not diminished, an additional 3 mg of d-tubocurarine were given, which produced adequate relaxation and approximately 90 percent depression of twitch tension. At the conclusion of a 2-hour procedure, 1.5 hours after the last curare dose, the muscle relaxant was antagonized with prostig-

mine, 1.5 mg, and atropine, 0.6 mg. An additional 0.5 mg of prostigmine and 0.2 mg of atropine were given subsequently before adequate return of neuromuscular function was documented by observation of twitch tension in the hypothenar muscles during ulnar nerve stimulation with a Block Aid monitor. The patient was extubated immediately postoperatively with no respiratory complications. Her postoperative course was uneventful and she was discharged from the hospital on prednisone 80 mg daily.

DISCUSSION

Despite steroid treatment sufficient to abolish the clinical symptoms of myasthenia, this case demonstrates the continued sensitivity of myasthenic musculature to d-tubocurarine. Although twitch tension was not recorded in this patient, Foldes states that after d-tubocurarine chloride, the response to indirect stimulation is markedly reduced in myasthenia gravis so that visual observation of the twitch will suffice to enable diagnosis of myasthenia gravis.[2]

While anticholinesterase drugs have long been the mainstay of treatment for myasthenia gravis, Torda and Wolff[3,4] in 1944 first showed that corticotropin could improve muscle strength in myasthenia gravis and that ACTH augmented the ability of tissue to synthesize acetylcholine. The disadvantages of corticotropin therapy, however, were an initial exacerbation of muscle weakness, an improvement which lasted only a few weeks to a few months, the frequent requirement for repeated courses, and the necessity for parenteral administration of the corticotropin.

In an effort to avoid the initial exacerbation seen with corticotropin therapy,[5,6] Warmolts and Engel[7] reported long-term use of a high single dose (100 mg) of oral prednisone every other day following withdrawal of anticholinesterase medication. Although others[8] have maintained anticholinesterase therapy, cessation of anticholinesterase therapy is frequently possible after steroid treatment. Decreases in steroid doses are often possible, but rarely can patients be maintained without at least small amounts of steroids.[9]

Despite the widespread use of steroids in myasthenia gravis, there have been no reports of the responses to nondepolarizing muscle relaxants during therapy except that of Griggs et al,[1] who studied an 8-year-old male patient who showed no sensitivity to 20 μg/kg of curare during ACTH infusions, but was sensitive to only 2.5 μg/kg of curare upon withdrawal of ACTH. Our patient, after 2 months of steroid therapy, had a response to curare (a decrease in twitch of approximately 50 percent) typical of a positive curare test.[2,10] After 4 months of therapy, she required 6 mg curare for sigmoid colectomy and 2 mg prostigmine to antagonize it 2 hours later. Whatever the mechanism of action of steroids in myasthenia gravis, they clearly do not result in sufficient acetylcholine at the neuromuscular junction, or adequate numbers of acetylcholine receptor sites, to require a usual dose of nondepolarizing muscle relaxant for competitive antagonism and neuromuscular blockade.

ACKNOWLEDGMENT

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Asystole In An Adult After a Single Dose of Succinylcholine

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CARDIAC asystole occurred in a normal adult following a single IV dose of succinylcholine.

CASE REPORT

A 24-year-old female with suspected appendicitis was brought to the operating room for abdominal exploration. Preoperative physical examination revealed right lower abdominal tenderness and low-grade fever. The patient had a leucocytosis of 14,000. Her serum potassium was 4.4 mEq/L (normal range is 3.5 to 5.0 mEq/L). Physical examination, history, and laboratory values were otherwise within normal range.

The patient was not premedicated. Blood pressure by auscultation was 110/80, heart rate was 90 beats/min, and continuous ECG monitoring showed regular sinus rhythm. Innovar®,§ 1 ml, was administered intravenously. The patient was preoxygenated with 100 percent O_2 by mask. Five minutes later, d-tubocurarine, 3 mg IV, followed by sodium thiopental, 50 mg IV, was given. Pulse rate and blood pressure did not change after this "test" dose of thiopental. Thiopental, 175 mg IV (3 mg/kg), was then given, followed in 1 minute by succinylcholine, 90 mg IV (1.5 mg/kg). Within 60 seconds the patient developed a sinus bradycardia with progression to complete sinus arrest noted by ECG. Heart sounds were no longer heard with the precordial stethoscope. She received a sharp, quick, single blow over the midportion of the sternum, ie, "precordial thump," was given atropine, 0.4 mg IV, was laryngoscoped, intubated with an endotracheal tube, and ventilated with 100 percent O_2. Sinus rhythm returned during laryngoscopy and intubation, 15 seconds after the sinus arrest was first noted. Return of sinus rhythm was not preceded by nodal or ventricular escape beats. The operation proceeded uneventfully. Abdominal exploration was negative.

Postoperative enzyme studies (serum creatine phosphokinase, lactic dehydrogenase, serum glutamic oxaloacetic transaminase) and serial ECGs were within normal limits.

DISCUSSION

In adults, cardiac arrhythmias following succinylcholine have been reported after repeated doses of the drug.[1,2] Arrhythmias have also been reported after a single dose in adult patients taking digitalis,[3] following massive trauma,[4] after burn injuries,[5] and in patients with neuromuscular disorders.[6,7] Bradyarrhythmias may follow a single dose of succinylcholine in healthy children.[8] Arrhythmias following succinylcholine have been attributed to increases in serum potassium, to postganglionic sympathetic stimulation, and/or to a direct myocardial effect of succinylcholine similar to that produced by acetylcholine.[9]

Studies have suggested that administration of a nondepolarizing muscle relaxant or an anticholinergic agent prior to a 2nd

§Innovar = fentanyl 0.05 mg + droperidol 2.5 mg/cc (McNeil Laboratories, Inc., Fort Washington, Pennsylvania 19034).

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dose of succinylcholine decreases the incidence of arrhythmias.[8,10] Evers et al[11] reported a 20 percent incidence of bradyarrhythmias following a single dose of succinylcholine in normal adults. List[1] reported a 40 percent incidence of bradycardia in his series of adults and children, and 2 of his patients developed asystoles of 5 and 14 seconds respectively after a 2nd dose of succinylcholine. He does not mention the ages of these patients. No reports, however, have been published of asystole in a healthy adult following a single injection of succinylcholine.

Innovar increases vagal tone.[12] Therefore, the concomitant use of Innovar and succinylcholine may have contributed to our patient's asystole.

This case is presented to alert the anesthetist that sinus arrest with asystole may occur after a single dose of succinylcholine in adult patients despite pretreatment with a nondepolarizing muscle relaxant.

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Covert Seizures as a Cause of Postoperative Apnea

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MANY conditions may cause or contribute to a failure of adequate ventilation at the completion of surgery. The following is a case report of a patient who became apneic after the resumption of adequate respiration at the completion of surgery. The cause was obscure. A physical examination at this time documented a seizure with minimal systemic manifestations. Respiratory support during the period of apnea was the only therapy provided.

CASE HISTORY

A 12-year-old, 44 kg, severely retarded, white female was admitted for an elective hysterectomy because of inability of the child or parents to maintain proper hygiene during menses. The patient was first evaluated at 2½ years of age for massive spasms. At that time her EEG showed a hypsarrhythmia pattern. As she grew older, she had both grand mal and petit mal seizures. On the day prior to surgery, she had 3 seizures in spite of her routine anticonvulsive therapy, consisting of diphenylhydantoin 100 mg twice a day, primidone 250 mg twice a day, diazepam 5 mg twice a day, and metharbital 50 mg 3 times a day. Physical examination prior to surgery revealed an uncommunicative patient with generalized

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motor incoordination. There were no other pertinent physical findings. Laboratory studies were within normal limits.

On the day of surgery she was given atropine 0.4 mg and morphine sulfate 10 mg IM 45 minutes prior to induction of anesthesia. She received no anticonvulsive therapy prior to surgery. Anesthesia was induced using N_2O, O_2, and halothane. The halothane was discontinued after an IV route was established. Pancuronium 4.5 mg was then administered with supplementation of 67 percent N_2O by 18 mg of morphine sulfate (0.4 mg/kg). An endotracheal tube was inserted without difficulty. Ventilation was controlled using a volume ventilator set to deliver a tidal volume of 0.65 L at a rate of 15/min. One hour after induction an additional 2 mg of pancuronium was administered IV. The operative procedure was completed in 135 minutes. During skin closure, controlled ventilation was discontinued, and the patient began to make spontaneous respiratory efforts. At completion of the operation the N_2O was discontinued and atropine 0.9 mg with neostigmine 2.7 mg was administered IV. The patient became responsive and helped with extubation. At this point respirations were spontaneous and adequate with a good airway and no evidence of hypoxia. As preparations were made to transfer the patient to the recovery room, spontaneous respiratory efforts ceased. Oxygen was administered by bag and mask. The blood pressure and pulse were unchanged. The pupils were checked and both eyes were found deviated to the right. Spontaneous respirations resumed 90 seconds after the beginning of the apneic spell, and the eyes returned to the midline position. She was taken to the recovery room and 60 minutes later transferred to her hospital room, fully responsive. Later that day she had focal seizures similar to the one in the operating room. The parents confirmed that one variation of her seizures was loss of consciousness with deviation of the eyes to the right.

DISCUSSION

Common causes of postoperative apnea include intraoperative hyperventilation, inadequate reversal of muscle relaxant, inadequate reversal of narcotic, and hypothermia. Seizures may produce postoperative apnea, but they should usually be easily recognized as the cause. In the case presented, apnea was the only apparent expression of an otherwise covert seizure until examination revealed deviation of the eyes to the right. Hyperventilation was excluded as a cause after return of spontaneous respirations. Although recurring apnea may appear after narcotic anesthesia, adequate respirations followed by the abrupt cessation of breathing support a seizure as the cause in this case. Morphine sulfate, extensively used in our practice up to a dose of 0.4 mg/kg in procedures lasting over 2 hours, has not produced postoperative apnea. Furthermore, it is unlikely that ventilation with O_2 alone for 90 seconds would have been the only therapy required in narcotic-induced apnea. The same can be said of inadequately reversed muscle relaxant, in this case pancuronium, given routinely in an initial dose of 0.1 mg/kg. Recurarization without overdosage of relaxant after adequate reversal of the block with neostigmine probably does not occur except when gallamine is used in patients with renal disease.[1] Postoperative apnea in the neonate may be caused by moderate hypothermia, which would not apply in this case. Delayed apnea with cyanosis may occur in children under 6 years of age during breath-holding spells.[2]

Difficulty in management may arise if it is not recognized that apnea may be the only expression of a seizure. The following classification of epileptic seizures is helpful in understanding atypical seizures. Seizures can be divided into the major categories of partial and generalized seizures.[3] Generalized seizures are easy to identify when they are accompanied by generalized symmetrical, tonic, or clonic motor behavior without local onset, eg, as in the classic grand mal seizure. Petit mal, atonic, and akinetic seizures are included in this group even though they may not have systemic manifestations. Partial seizures are seizures beginning locally or focally in the brain and may be either elementary in symptomatology, usually without impairment of consciousness, or complex; the latter may be associated with loss of consciousness with temporal lobe or psychomotor seizures. Except for petit mal and similar seizures of the generalized type, partial seizures of any variety without motor behavior are difficult to recognize. The patient presented had partial (focal) seizures with motor signs of the Jacksonian type (eyes deviated to the right). Recognition of partial seizure activity is particularly difficult in the immediate postoperative period since there may be a masking or modification of this activity by the anesthetic.

Scalp EEG monitoring of seizure disorder patients, although cumbersome, might be helpful, but correlation of abnormal cerebral activity with behavior is at times difficult even in the unanesthetized patient.

Management in the operating or recovery room should consist of maintenance of airway and ventilation and avoidance of unnecessary therapy for other causes of apnea. Specific therapy for better control of the seizure disorder, if necessary, can usually be accomplished later.

SUMMARY

Covert seizures expressed as apnea may occur in the immediate postoperative period, and they should be suspected particularly in the known seizure-disorder patient. Management includes ventilation with O_2 and avoidance of inappropriate administration of reversal drugs.

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Pain and Cluneal Neuropathy Following Intragluteal Injection

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SCIATIC nerve injury is a recognized complication of faulty intragluteal injection. It is commonly manifested by paresis in the sciatic distribution and may be followed by causalgialike pain in the extremity several hours or days later. Motor function is more profoundly affected than sensory, and motor recovery is less complete.[1,2] In contrast, this report describes 2 cases in which improper intragluteal injections resulted in chronic aching pain and altered sensation of the buttock without evidence of motor involvement. We have been unable to find this reported in the literature.

REPORT OF TWO CASES

Case 1—A 60-year-old woman received several IM injections of gentamicin into the medial inferior quadrant of the right buttock. After 2 days, she experienced burning pain at the site of injection radiating to the posterior thigh and knee. The pain persisted and was present unabated at the time of our examination 18 months later. At no time were there complaints of weakness. Examination revealed tenderness to pressure over the sciatic notch. There was hyperesthesia to pin scratch and decreased touch sensation over the right inferior buttock corresponding to the distribution of the inferior cluneal nerves. The remainder of the examination as well as electromyograms of the lower extremities were within normal limits. There was neither a positive Trendelenburg sign nor distal weakness.

In an attempt to localize the lesion, a spinal needle was inserted into the area of tenderness and connected to a nerve stimulator.§ The tip was presumed to lie within the piriformis muscle. Stimulation reproduced the patient's pain. Subsequent injection of 5 ml 1 percent lidocaine resulted in hypalgesia of the mid to lower buttock corresponding to the upper portion of the hyperesthetic zone. The needle was repositioned more medially into the piriformis

§Burroughs Wellcome Peripheral Nerve Stimulator

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muscle; stimulation again resulted in paresthesia in the painful area. Injection of 2 ml 1 percent lidocaine produced hypalgesia of the remaining hyperesthetic area. Both procedures reduced pain approximately 25 percent. After 5 years, the patient's pain has persisted but is controlled with propoxyphene.

Case 2—An 18-year-old girl received an intragluteal injection of hydroxyzine in the upper outer quadrant of the left buttock while leaning forward over a stretcher. She immediately experienced sharp pain radiating from the buttock to the foot and stated that she could not bear weight on the leg. On examination the following morning, no loss of motor power was found. Aching pain continued, became localized to the injection site, and persisted for 2 years. On our examination at this time, nonradiating pain increased with deep pressure over the sciatic notch. Pin-scratch dysesthesia was noted over the middle and inferior left buttock corresponding to the distribution of the inferior cluneal nerves. The remainder of the examination was within normal limits. Stretching of the piriformis muscle by forced internal rotation of the thigh in extension did not increase pain.

In an attempt to delineate the anatomical substrate of dysesthesia, block of the superior cluneal nerves was accomplished with lidocaine injection at the posterior iliac crest. This resulted in analgesia of the upper buttock, above and bordering on the dysesthetic area. No pain relief was obtained. Therefore, the needle was reinserted into the pressure trigger point of the buttock. While connected to a nerve stimulator, the needle was manipulated until the patient's typical pain was exacerbated. There was no evidence of distal paresthesia or motor response with stimulation. The needle tip was thought to rest within the piriformis muscle. Injection of 10 ml 1 percent lidocaine resulted in immediate pain relief and analgesia of the previously dysesthetic zone. Pain was abolished for 3 days, then returned to a lesser degree. During the period of pain relief, a pin-scratch deficit (hypalgesia) persisted in the distribution of the inferior cluneal nerves, but without painful dysesthesia. One week later, injection into the piriformis muscle was repeated with the same result. Complete pain relief lasted more than 2 months. Soreness then returned to the same area, but was present only with vigorous activity. This was not judged by the patient to be severe enough to require treatment.

COMMENT

The sciatic nerve passes out of the pelvis through the greater sciatic foramen from beneath the piriformis muscle and descends between the tuberosity of the ischium and the greater trochanter. Its exit corresponds to a point on the skin about 4 cm down on the perpendicular bisecting the line connecting the greater trochanter and the posterior iliac spine. To avoid damage to the nerve, intragluteal injections should be administered in the lateral aspect of the area above this connecting line,[3] with the patient in the prone position.[2] In our 1st patient the injections were clearly given below the recommended area; in the 2nd patient the standing position with forward flexion had been employed. This maneuver may distort the anatomy so that a needle placed into the apparent upper-outer quadrant may, in fact, lie in the piriformis muscle or even approach the sciatic nerve.[4] However, our patients developed chronic aching pain and dysesthesia in the distribution of the inferior cluneal nerves without evidence of motor loss. This cannot be explained on the basis of a sciatic nerve injury.

The skin of the buttock is innervated by 3 groups of nerves: the superior cluneal nerves from the dorsal rami of L_1-L_3 (superior and mediolateral portion); the middle cluneal nerves from S_1-S_3 (medial portion); and the inferior cluneal nerves from the posterior femoral cutaneous nerve (inferior portion). The posterior femoral cutaneous nerve is a direct branch of the sacral plexus and has only sensory function. Its course parallels the sciatic nerve and crosses this nerve from ventromedial to dorsal as it passes from beneath the piriformis muscle. Immediately upon exiting from the pelvis, it gives off the inferior cluneal nerves which round the lower border of the gluteus maximus muscle to reach the skin of the lower buttock (fig 1). Further branches supply part of the perineum and the skin of the back of the leg to below the popliteal fossa.[5]

Since the posterior femoral cutaneous nerve may run dorsal to the sciatic and the clunei may branch off very early in its course,[6] these nerves may be directly injured by faulty intragluteal injection. The dorsal portion of the posterior femoral cutaneous nerve which furnishes the inferior cluneal branches may traverse the piriformis muscle[6] (fig 2). It is likely that this was the case in our patients, as block of the inferior

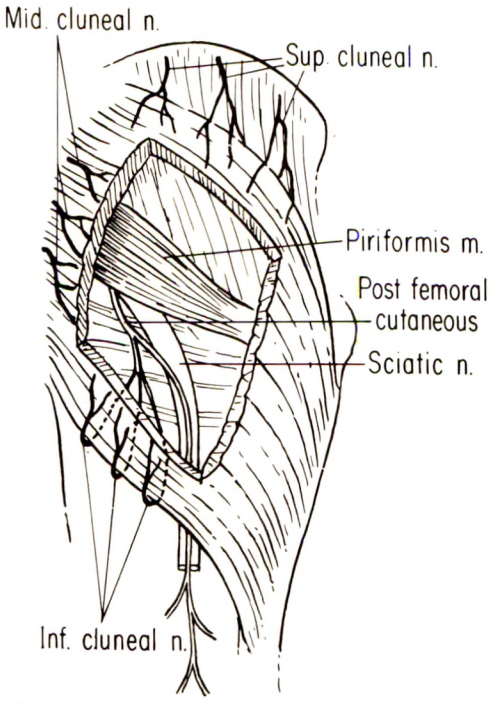


FIG 1. The deep anatomy of the gluteal region through a window in the gluteus maximus. The posterior femoral cutaneous nerve runs dorsal to the sciatic after these nerves exit the infrapiriform foramen. The inferior cluneal (branches of the posterior femoral cutaneous), superior cluneal, and middle cluneal nerves are shown (according to Hollingshead[5]).

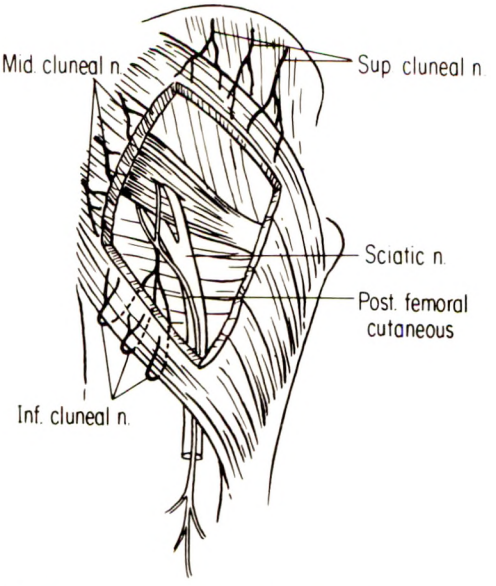


FIG 2. An anatomic variation of fig 1; the dorsal portion of the posterior femoral cutaneous nerve (supplying the inferior cluneals) and the peroneal division of the sciatic nerve traverse the piriformis muscle (according to Shaeffer[6]).

cluneal nerves resulted from the injection of a local anesthetic into the piriformis. Injection of an irritating substance into the muscle, therefore, may have resulted in a chemical neuritis. Damage to a purely sensory nerve may be manifested by pain and altered sensation evident on pin-scratch examination as in our patients.

Gluteal and posterior thigh pain may also result from spasm of the piriformis muscle. This was proposed after cadaver dissection demonstrated that tightening of this muscle results in compression of the sciatic nerve between the muscle belly and the sacrospinous ligament.[7] A piriformis syndrome has been described to explain some cases of obscure sciatica,[8] and may have accounted for some of the initial pain reported by the 2nd patient. Muscle spasm and myositis may result from IM injection,[4] and entrapment of nerves within the muscle may ensue. In our cases, permanent mechanical damage may have resulted to the inferior cluneal nerves during their course through the piriformis.

It may be argued that the observed sensory alterations in the buttock were inconsequential to the persistence of pain. Rather, pain may be explained on the basis of a myofascial syndrome triggered by the IM injections. Myofascial syndromes are characterized by trigger points, upon which pressure produces distant pain. Injection of a local anesthetic into the trigger point abolishes pain temporarily and may even be curative.[9] Our patients exhibited trigger points localized to the piriformis muscle; the injection of local anesthetics abolished pain, partially in 1 case and completely in the other. However, as the injections also produced analgesia of the inferior cluneal nerves, it is not possible to determine whether the primary cause of pain was neuralgia or a myofascial syndrome.

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An isolated pheochromocytoma was removed from a 14-year-old boy. The tumor was shown to secrete noradrenaline predominantly. In addition to severe hypertension, the patient demonstrated metabolic abnormalities which included elevated free fatty acid levels, depressed insulin levels, hyperreninemia, hypercalcemia, and hypercalciuria with normal parathyroid function. All abnormalities returned to normal after tumor removal. It is suggested the metabolic effects of the tumor were the result of β-adrenergic stimulation by noradrenaline. *(Passwell J. Boichis H, Lotan D, et al: The metabolic effects of excess noradrenaline secretion from a pheochromocytoma. Am J Dis Child 131:1011-1014, 1977)*

Correspondence

WARMING POVIDONE-IODINE SOLUTION FOR SKIN PREPARATION

To the Editor:

The warmer for skin preparation solutions described by Restall and Schmidt[1] is designed to warm 1:1000 thimerosal and 70 percent alcohol to 40° C. It is recommended[2] that povidone-iodine (Betadine®) not be warmed in this way, but that it be used at room temperature since the potential benefit to the patient may not be worth possible loss of potency resulting from repeated or sustained heating to 40° C.

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* * *

NITROPRUSSIDE AND CEREBRAL BLOOD FLOW

To the Editor:

Stoelting et al[1] state in their article on sodium nitroprusside (SNP)-produced hypotension during surgery in the head-up position that "there is evidence that SNP may maintain CBF (cerebral blood flow) during hypotension." This is indeed supported by the work of Stoyka and Schutz,[2] who demonstrated that CBF remained similar to baseline values during SNP-induced hypotension to a mean arterial pressure (MAP) of 30 torr. Additionally, Waltz[3] found in cats and Griffiths et al[4] in man that there were no significant changes in CBF despite large decreases in MAP during SNP administration.

On the other hand, however, Carter and Atkinson[5] reported a 24 percent decrease in CBF associated with an SNP-induced decrease in MAP of 25 percent using a thermal diffusion technic in cats. Crockard et al[6] noted a 16 percent decrease in CBF with a 5 percent decrease in MAP when giving SNP to rhesus monkeys. Greater degrees of hypotension were associated with further decreases in CBF. Brown and collaborators[7] also showed a significant fall in CBF in awake humans with small reductions in blood pressure during infusion of SNP.

In view of these data, one should consider the possibility that SNP may have effects on CBF and, consequently, intracranial pressure (ICP) which differ in patients with pre-existing impairment of cerebrovascular autoregulation or elevated ICP. Therefore, sudden variations in MAP induced with SNP may exceed the capacity of the cerebral circulation to autoregulate its flow, as suggested by the work of Turner et al.[8] These rapid increases and decreases in MAP might be associated with significant changes in CBF and cerebral blood volume, placing the neurosurgical patient with increased ICP and vascular pathology at greater risk.

The combination of these swings in MAP with an increase in ICP produced by the SNP itself (Keykhah, personal communication) may be of particular importance when SNP is initiated or stopped abruptly at the cessation of induced hypotension. For these reasons, we have introduced the use of parenteral nitroglycerin in neurosurgical operations to adjust MAP to normotensive or hypotensive levels.

It would appear, therefore, that the effects of SNP on CBF are not yet fully defined. Further study is indicated to elucidate the actions of this important drug.

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STATISTICAL ANALYSIS OF pH DATA

To the Editor:

Easy access to computers has encouraged researchers to use statistical tests with which they are unfamiliar, tremendously increasing the potential for mistakes. Research involving pH data seems to be especially prone to such mistakes. Table 4 of Minuck and Sharma[1] provides an example of this problem. Because of statistical errors, the accuracy of the means and standard deviations is questionable and the comparisons between treatments are invalid.

Most researchers know that pH = $-\log [H^+]$, but there is a difficult conceptual jump from that memorized fact to a realization that pH values will have a lognormal distribution. However, this concept is critical, because the arithmetic mean, standard deviation, and standard error, as well as such statistical tests as analysis of variance (ANOVA), correlation, and regression, assume that the data is normally distributed. This problem is compounded by the fact that statisticians use synthetic data to develop and test new statistical procedures. As a result, the use of a statistical test on data from the "real world" always requires more judgment and involves more uncertainty than is commonly appreciated. The purpose of this letter is to describe an analysis protocol that may help researchers avoid such mistakes.

The first step in the analysis of pH data should be to convert all pH measurements to $[H^+]$ and then calculate a mean, standard deviation, and, if desired, a standard error. These values can then be reconverted to pH units. Deviations calculated in this manner will be asymmetrical; therefore any published pH values with symmetrical confidence limits have probably been calculated incorrectly.

Once this has been done, the researchers will usually want to compare group means (such as between treatment and control groups) and test for significant differences. This has traditionally been done with ANOVA, but if the Kruskal-Wallis test (Zar, 1974[2]) is used, it will provide the same information, but is free of assumptions about normality or equality of variances.

Before the researcher can use ANOVA, the data should first be tested for equality of variances. This is a critical assumption and one which most biological data will violate. The F-Max test (Sokal and Rohlf, 1969[3]), which measures this, is very simple; it will provide a quick and easy method for identifying data that *must not* be analyzed by ANOVA because treatment and control group variances are unequal.

In the event that the variances are equal, the data should still be tested for normality before proceeding with the ANOVA. A sample size of about 30 is the minimum necessary for such a test to work properly and many experimenters will not have this large a sample. A computer program nevertheless will test for normality with fewer than 30 items, but then an answer of "not significantly different from normal" reflects the inadequacy of the test, not a statement of reality. ANOVA should be used only after the data is known to be normally distributed, with equal variances.

The development of statistical tests that are less restrictive about the data they can use is an active area of biometrics research, so this has been a shallow discussion of a complex issue. My hope is that it will give

your readers a feel for what questions to ask a biometrician.

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MORE ABOUT INTUBATION OF PATIENTS WITH FULL STOMACHS

To the Editor:

The recent article by Dr. Cucchiara[1] on esophageal intubation for control of gastric contents and the reply of Dr. Roberts[2] have served as important reminders of a valuable procedure in the anesthetic management of patients with full stomachs.

However, their historical documentation is not complete. In 1957 Drs. Giuffrida and Bizarri[3] advocated the use of esophageal blocking and diversion of gastric contents by use of a special tube.

In 1966[4] I advocated having available 2 endotracheal tubes during endotracheal intubation of patients with full stomachs. One tube could be inserted into the esophagus if regurgitation occurred; then the 2nd tube could be inserted into the trachea after clearing the throat. This "two-tubes" technic has been a part of our program in managing general anesthesia for patients with full stomachs for several years. Fortunately the need for the esophageal intubation has been rare, when the other precautions are employed, including use of the head-up position, preoxygenation, avoidance of positive-pressure ventilation, cricoid pressure, and pretreatment with competitive neuromuscular blocking agents prior to the use of succinylcholine before intubation.

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PEEP MEASUREMENT

To the Editor:

In the description by Drs. Weeks and Comer of a PEEP device for anesthesia circuits[1] it is stated that PEEP is reflected by the canister pressure gauge on the Ohio circle system. I have not found this to be true. PEEP pressure must be measured with a manometer inserted distal to the inspiratory valve and proximal to the PEEP valve in the Ohio circle system. Perhaps the authors interchanged the description of the Ohio and Foregger circle systems.

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REFERENCE

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To the Editor:

I owe an apology to the readers of ANESTHESIA AND ANALGESIA and an expression of gratitude to Dr. Glick for pointing out an error in our paper, "A PEEP Device for Anesthesia Circuits."

All of the observations reported are true and valid, with one exception. The values of PEEP in the patient circuit which were recorded on paper as well as back pressures reflected in the anesthesia machine are as stated. The error concerns the statement that PEEP values may be read from the canister pressure manometer of the Ohio machine, #20 carbon dioxide canister. The only model that I could find which would reflect PEEP is the Ohio #18 canister manometer. So long as the manometer is not on the patient side of the directional valves, PEEP, which is present if applied as sug-

gested, will not be measured by the canister manometer. Our error was in transcribing data to our draft and was subsequently overlooked, since we had turned our attention to back pressure phenomena in the anesthesia machine. In conclusion, if the Boehringer model 4801 PEEP valve is placed vertically as directed in the appropriate place in the system used, PEEP is faithfully produced; the measurement, however, may not be reflected in a gauge located outside the patient's circuit.

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* * *

PARAVERTEBRAL SYMPATHETIC BLOCK

To the Editor:

I read with interest the article by Dr. Fujita et al on the effect of chemical sympathectomy on muscle blood flow.[1] Their technic of chemical sympathectomy involved placement of four 21-gauge needles lateral to the midanterior spinal corpora of the 1st to 4th lumbar vertebrae under fluoroscopic control. Accurate positioning of the needle was confirmed by the injection of Urographine at each level. Four to six ml of 5 percent phenol in glycerin were then injected and the patient kept in position for 1 hour. The authors also stated that the spread of local anesthetic solution could be easily controlled by positioning of the patient.

Suggestions regarding the proper technic of temporary and permanent lumbar sympathetic blockade have already been published in this journal.[2] The technic involves the taking of a scout PA x-ray film of the lumbar spine with an 18-gauge needle positioned on the skin at the upper edge of the 2nd lumbar spinous process. After identifying the proper level, the skin is prepared with an antiseptic solution and draped in a sterile manner. A skin wheal is raised 5 to 6 cm lateral to the upper edge of the spinous process of the second lumbar vertebra.

A 20-gauge, 12.5-cm needle is then placed through the skin wheal and contact made with the transverse process of the 2nd lumbar vertebra. The marker on the needle is set a distance of 3 to 4 cm from the skin surface before redirecting the needle medially and cephalad so that it slides off the upper border of the transverse process and the lateral aspect of the vertebral body. By sliding the needle off the upper border of the transverse process, painful paresthesias to the lateral thigh (L-2) are avoided. The position of the needle is verified by PA and lateral x-ray films before injection of 10 to 20 ml of anesthetic solution.[3]

Using the classical approach, a single needle with its tip at the anterolateral aspect of the 2nd lumbar vertebra is sufficient to precisely and reliably block the lumbar paravertebral sympathetic chain. The postganglionic sympathetic outflow to the lower extremity is primarily through the 1st and 2nd lumbar sympathetic ganglia;[4] hence, interruption of pathways below this level is unnecessary. Multiple needle placement as described by Fujita et al predisposes to a greater likelihood of complications and increased patient discomfort. The volume of neurolytic solution injected can be kept at a minimum. Table tilt or gravity does not influence the spread of injected solution since the sympathetic chain lies in a potential fascial plain. Finally, prior to permanent neurolysis, a diagnostic block using local anesthetic should be performed. This procedure is also of prognostic value.

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ANTACIDS AND GLYCOPYRROLATE

To the Editor:

It is unfortunate that Dr. Baraka and his colleagues[1] allowed their enthusiasm for the anticholinergic drug glycopyrrolate to cause them to disparage methods previously also

found to be effective. I refer particularly to the sentence, "The oral administration of antacids to alter the pH of gastric contents prior to induction of anesthesia in parturients has resulted in severe pulmonary complications and in delayed emptying and retention of gastric contents." This sentence implies that antacids caused the severe pulmonary complications. The case they quote, that by Taylor,[2] was one of acid aspiration pneumonitis occurring in a patient in whom the pH of gastric contents sampled 20 minutes following the episode was 3.5. The point made was that although the antacid had raised the pH above 2.5, a level hitherto commonly accepted as critical, this patient still developed acid aspiration pneumonitis. Presumably the result would have been the same had the pH been raised to 3.5 by glycopyrrolate. The patient, however, recovered. One wonders how well the patient would have fared had no antacid been given and had the pH been lower than 3.5.

There is little evidence that antacids delay the emptying of the stomach; in fact, there is considerable evidence to the contrary. An increase in gastric pH has an effect mediated by the release of gastrin which results in an increased tone of the gastroesophageal sphincter.[3] Dundee[4] has demonstrated more rapid absorption of oral diazepam when given with antacids, suggesting more rapid movement of diazepam into the small intestine. In the first definitive report on the use of antacids published in the United States, Roberts and Shirley[5] showed that the mean volume of gastric contents following the administration of antacids was slightly lower than the mean volume in those patients who did not receive antacids.

Glycopyrrolate may yet be a further valuable addition to the long list of requirements needed to prevent aspiration pneumonitis. The patient's cause, however, is not helped by disparaging one preventive technic in order to promote another. Provided at least 60 minutes are available before delivery, glycopyrrolate may be an additional valuable tool. It does not replace the established use of oral antacids as a preventive measure against aspiration pneumonitis.

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VENTILATORY PATTERN

To the Editor:

The paper by Downs et al[1] was read with interest. The strip chart recordings presented in fig 2 of that paper are especially informative. Although the end-expiratory pressure level during intermittent mandatory ventilation (IMV) was progressively increased from 0 through 5 to 10 cm H_2O, *mean* intrapleural pressure exhibited only a minor variation, from −3.49 through −2.59 to −1.68, respectively. The strip chart recordings demonstrate that this coincided with progressively more vigorous spontaneous inspiratory efforts on the part of the patient. It is not surprising, therefore, that cardiac output was unchanged despite an increase in end-expiratory pressure.

On the other hand, one is struck by the marked degree of hyperventilation imposed during the period of intermittent positive pressure ventilation (IPPV). Dr. Craig's guest discussion makes reference to the fact that the intercurrent hypocapnia precludes any valid comparison between the cardiovascular effects of IMV and IPPV. Dr. Craig's caveat is absolutely correct but perhaps should be stated more forcefully. The studies of Breivik and coworkers reveal that a change in $Paco_2$ from 25 to 35 torr resulted in a 32 percent increase in cardiac output during controlled ventilation of patients with pneumonia.[2] In this light, the reduction in cardiac output observed by Downs and associates during IPPV appears very modest, amounting to only about 12 percent, when one considers the appreciable change in $Paco_2$ observed (from 44 to 29 torr). The study of Breivik et al[2] was listed as a reference in the report by Dr. Downs that originally described IMV.[3] It is un-

fortunate that the enlightening and extremely pertinent data of Breivik's group were not referred to in the recent report.[1]

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VAPORIZERS FOR ETHER

To the Editor:

Further to my Brief Report[1] on the use of a Bird® ventilator as a demand-feed anesthetic machine, I have successfully used a Cyprane® Chlorotec vaporizer charged with diethyl ether in this circuit. The limited duration of drawover (± 33 percent of elapsed time) allows good heat exchange. Multiplying the percent setting on the Chlorotec by a factor of 2.5 gives the approximate delivered ether concentration.

In 39 patients I have so far found that ± 5 percent ether is ample for maintenance, and that a single charging of the vaporizer is sufficient for more than 1 hour of anesthesia.

A simple scavenging system[2] only leaks flammable waste to the environment when the vaporizer is delivering ether concentrations in excess of 7.5 percent. There is some leakage through the control valve at higher settings.

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REFERENCES

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Effects of epidural analgesia on mother and infants were studied in 14 women with twin pregnancies. Maternal arterial and umbilical vessel blood gas and acid-base measurements, together with Apgar scores, were determined. Apgar scores and blood gas values for 1st twins were similar to singleton controls, while 2nd twin results showed deterioration, as previously reported. Lumbar epidural analgesia is recommended as a safe form of analgesia for labor and delivery of twins. *(James FM, Crawford JS, Davies P, et al: Lumbar epidural analgesia for labor and delivery of twins. Am J Obstet Gynecol 127:176-180, 1977)*

Questions and Answers

We invite you to submit questions to the Editorial Office, Anesthesia and Analgesia . . . Current Researches, Yale University School of Medicine, 333 Cedar St., New Haven, Connecticut 06510. The names of those submitting questions will remain anonymous if so desired.

The answers will be prepared by competent authorities, and their names will or will not appear, according to their specific wishes.

QUESTION: *As a Doctor of Dental Surgery on the staff of Taiwan University Hospital and College of Medicine, I am unclear about the role of a DDS in the field of anesthesiology. Is it legal for a DDS to be trained as and subsequently to function as an anesthesiologist?*

DDS, DA,
Taipei, Republic of China

ANSWER #1: Dentists were pioneers in the field of anesthesia and have continued to demonstrate their competence in management of both general and regional anesthesia for their patients. Some dentists are providing anesthesia for all types of surgery. It is "legal" for dentists to administer anesthetics and narcotics, as well as digitalis or antibiotics. For dentists to provide safe care for their patients they must be able to obtain a history, perform a physical examination, and interpret laboratory studies. They also should be skilled in resuscitation technics and emergency medical management. However, I believe that it is inappropriate for dentists to perform as specialists in cardiology, emergency medical management, or infectious disease control, just as I believe it is inappropriate for them to perform as specialists in anesthesiology. Dentists should limit their practice to anesthesia for dental patients or, where necessary, to the administration of anesthesia to surgical patients in association with a physician specialist in anesthesiology.

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ANSWER #2: In most states, it is not illegal for a dentist to be trained as an anesthesiologist. For a number of years, the University of Tennessee permitted qualified dentists to enter the anesthesia residency program. Standards were high, and only those who demonstrated competence were permitted to remain in the program. They were exposed to the same training and curriculum as the medical doctors. In recent years, only one DDS has completed the program. He was an oral surgeon who was interested in an instructional position with the College of Dentistry.

There are two basic problems with the training of dentists as anesthesiologists. The first is their lack of adequate medical background in areas not covered by the usual anesthesiology training program, ie, infectious disease, cardiology, gastroenterology, etc. However, it has been our experience that the motivated dentist, particularly if he stays in the program longer than the customary 2 years, acquires a satisfactory knowledge of these aspects of medicine.

The 2nd problem, more practical, has to do with the fact that, in many communities, poorly motivated, inadequately trained dentists pass themselves off as anesthesiologists (which implies a medical background) in a community, with consequent possible detriment to the level of anesthesia care in that community and adding to the economic difficulties of attracting well-trained anesthesiologists to the community. In our area of the country this has been a problem for both dentists trained in a conventional program and the graduates of conventional programs in anesthesiology.

A further problem is the fact that there is no national accrediting or certifying mech-

anism for such individuals, which precludes any estimate of their qualifications by hospital staffs, physicians, or patients. We have taken the position that for these reasons we will no longer accept anyone other than an MD into our training program unless a dentist is seeking special training, not to become a practicing anesthesiologist. When inquiries are made about dentists with anesthesia training, we point out that they are not anesthesiologists in the medical sense and that they have the limitations imposed by lack of undergraduate medical training.

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* * *

QUESTION: *Please comment on whether or not it is safe to use magnesium sulfate in treating toxemia of pregnancy in a woman with a family history of malignant hyperpyrexia.*

ANSWER #1: In the framing of the question, the pregnant woman is given a positive family history for malignant hyperthermia. Assuming that she is a susceptible individual, there is no evidence presently to show that the use of magnesium sulfate would be detrimental and cause a triggering of the syndrome during delivery. Since the toxemia obviously can be life threatening, it is reasonable to treat a patient for this with magnesium sulfate. In experimental pigs and in man, neither calcium nor magnesium injections have been reported as triggering the syndrome. Also, in the literature there has not yet been reported a full-blown case of malignant hyperthermia during anesthesia for delivery. There has been a report of a susceptible individual who developed a rise in creatine phosphokinase (CPK) during spinal anesthesia for delivery. This patient already had a markedly elevated preanesthetic CPK level, and her CPK remained elevated. She did not demonstrate any of the clinical symptoms of malignant hyperpyrexia. During the acute syndrome, magnesium and phosphate levels generally have been reported as elevated, whereas calcium determinations initially are elevated and later decrease sharply. It should be remembered that these are total levels measured in the plasma and may not reflect intracellular responses during the acute episode.

In summary, it would seem that there is no evidence to restrict the use of magnesium sulfate during delivery in a toxemic patient.

John F. Ryan, MD
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* * *

ANSWER #2: While considerable progress has been made in delineating the patterns, predisposing features, and treatment of malignant hyperpyrexia, the exact etiology remains unknown.[1,2] It has been suggested that the etiology may be a failure or reduction in the capacity of the sarcoplasmic reticulum to accumulate calcium and that the resulting elevated myoplasmic calcium activates phosphorylase kinase and myosin ATPase, stimulating glycolysis and producing phosphate and heat. The release of catecholamines, which is also calcium ion dependent,[3] can be envisaged to produce a vicious cycle in which the metabolic changes lead to catecholamine release and hence further metabolic changes.

Magnesium sulfate is still widely used in the management of toxemia of pregnancy,[4] although the mechanism by which the magnesium ion controls the convulsions is not completely understood. It is known that there is an action on the neuromuscular junction reducing the number of acetylcholine quanta released by the nerve action potential.[5] In humans susceptible to malignant hyperpyrexia, the serum magnesium level is in the low-normal range at rest,[6] while during a hyperpyrexial episode the serum magnesium, calcium, and potassium are all raised, as one might expect from the muscle lesion. Many of the actions of calcium are antagonized by magnesium, notably the effect on myosin ATPase and catecholamine release. In pigs, magnesium has been used successfully in the treatment of an established hyperpyrexial episode,[7] an experiment which might justify the use of magnesium as a prophylactic agent against a pyrexial episode in man. Magnesium has also been shown to potentiate the inhibitory effect of procaine HCl on calcium transport.[8] This might be an advantage in using procaine, which, with dantrolene, is the major

active therapy against established malignant hyperpyrexia.

Finally, it is clear that not all members of a family demonstrating the trait are equally susceptible to the condition. The caffeine contracture test of a muscle biopsy would indicate an unusually sensitive individual.[9] In this type of patient, adequate resuscitative measures should always be available against an unexpected reaction to any drug.[10]

The use of magnesium sulfate to treat toxemia of pregnancy is not contraindicated in this type of patient. Indeed, it may find a place in the prevention or treatment of hyperpyrexial episodes.

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The progress of labor and eventual outcome were studied in 698 patients receiving epidural analgesia with bupivacaine 0.125 percent with epinephrine 1:200,000. Epidural analgesia was started when the cervix was dilated 4 to cm and only after demonstration of progressive dilatation of the cervix. The epidural labor curves were characterized by acceleration in the rate of cervical dilatation and correlated well with the previously published curves for "normal" labor. The dilute concentration of local anesthetic used is postulated as one factor promoting maintenance of a normal rate of progress in labor. *(Phillips JL, Hochberg CJ, Petrakis JK, et al: Epidural analgesia and its effects on the "normal" progress of labor. Am J Obstet Gynecol 129:316-323, 1977)*

Books Received

Title	Author/Editor	Publisher	Price Pages
Pain in the Trigeminal Region	DJ Anderson B Matthews	Amsterdam, Netherlands Elsevier/North Holland 1977	$49.50 453 pp
Retro Spectro Scope	Julius Comroe	Menlo Park, California Von Gehr Press 1977	$5.00 186 pp
Malignant Hyperthermia: Current Concepts	Ernest O Henschell	New York Appleton-Century-Crofts 1977	$12.50 192 pp
Peripheral Nerve Block	FL Jenkner	Secaucus, New Jersey Springer-Verlag 1977	$10.00 116 pp
Veterinary Acupuncture	Alan M Klide Shiu H Kung	Philadelphia University of Pennsylvania Press 1977	$35.00 297 pp
Body, Mind, Behavior	Maggie Scarf	New York Dell Publishing Company 1977	$2.25 365 pp
Manual of Anesthesia	John C Snow	Boston Little, Brown and Company 1977	$12.50 547 pp
Dementia	Charles E Wells	Philadelphia FA Davis Company 1977	284 pp

Book Reviews

Costs, Risks, and Benefits of Surgery, edited by John P. Bunker, Benjamin A. Barnes, and Frederick Mosteller, 401 pp, $22.50, New York, Oxford University Press, 1977.

In the 1950's and early 1960's John Bunker, an anesthesiologist, was widely known for his pioneering studies of metabolic responses of man to anesthesia. Today, Dr. Bunker is equally well known for his many perceptive contributions to what can be described as the public health aspects of medicine, especially surgery and anesthesiology. The change in direction may have been due to the new vistas opened to him when he acted as editor and the chief driving force behind the famous National Halothane Study of 1969. This report, of far greater significance than its title suggests, not only presented extensive data on liver failure associated with anesthesia but also provided the first epidemiologically sound data on national mortality rates associated with anesthesia and surgery. Dr. Bunker followed the halothane report with equally valuable papers on factors affecting the frequency with which operations such as hysterectomy are performed. In the present book Dr. Bunker joins forces with Dr. Benjamin Barnes, a surgeon, and Frederick Mosteller, a statistician with considerable experience in matters anesthetic, to edit a series of papers dealing with evaluation of the costs (financial and societal) as well as the risks and benefits (or lack thereof) which may be associated with surgery.

This is an important book for anesthesiologists. It is important in part because of the objective data it provides on the costs of operations ranging from appendectomy, mastectomy, and hysterectomy to coronary bypass and renal transplant. Not just apparent costs, either. The analysis includes subtle and direct costs of surgery as well as obvious costs such as those related to hospitalization and surgical fees. Costs are then compared to benefits, potential and real. One learns, for instance, there is good reason to doubt that elective repair of inguinal hernias is really superior to use of trusses in terms of dollars, comfort, or prolongation of life. One also learns that if each of the estimated 368,000 persons in the United States with silent gallstones were operated on (it would cost $543 per case or a total of $200,000,000 dollars to identify them), the cost of operating on these patients would amount to an additional $1.1 billion dollars. This would prolong life by one or two weeks. Similarly, if each adult American male paid a premium of $20 to $45 per year throughout his life, the costs of performing coronary artery bypass operations nationally would be covered. The benefit would be prolongation of life by approximately three-quarters of a day per year.

These and similar types of cost accounting are increasingly being applied throughout medicine. They have to be. Demands for medical services and the costs they generate cannot increase indefinitely, not, that is, unless the American citizen will no longer even be able to afford a car because of the cost of medical care. *That* will really bring about a reordering of priorities.

Cost accounting is being applied not only to surgery. It should and will include anesthesiology. This will involve close scrutiny of many of the procedures and practices we so routinely rely upon today. What, for example, are the costs of ordering routine ECGs in all patients above the age of, say, 45? What, in quantifiable objective terms, are the benefits derived from such a practice? What are the costs of routine preoperative chest x-rays? What are the benefits? We do these types of things, but where are the data to quantitate either the expenses involved or the benefits accrued? We are increasingly going to be required to *prove* that what we advocate as good clinical practice is based on something more substantial than good will, pious hope, or a visceral sensation that what we do *ought* to be good for the patient. Dr. Bunker and his associates describe in detail why new and radical approaches to evaluation of costs and benefits are so necessary. They also show how one can go about making cost-benefit

analyses and, thereby, making rational rather than subjective decisions as to what we do and do not do.

The book does not deal solely, however, with costs in terms of dollars and what these dollars buy in terms of prolongation of life. Quite the contrary. The book also addresses itself to the equally important matter of the quality of life enjoyed or not enjoyed following certain operations, as well as, for that matter, the quality of life provided when surgery is not performed. Mortality rates alone are not the sole index of surgical success. What avail is it if surgery allows a patient to live an additional year if he is so miserable that he wishes he were dead each day of the year? Difficult questions arise when one attempts to quantitate something as complex as the quality of life, but it is most encouraging to see that matters as complex as these are being addressed and that they are indeed susceptible to objective study and to presentation as quantifiable data which allow us to make reasoned decisions as to which form of therapy may be best for our patients.

Reading this book is not always easy. It starts off with 105 pages of background and general principles of cost-benefit and decision analysis. It then applies these principles to both established and new surgical procedures. But the effort involved in working one's way through the principles and methods of cost-benefit and decision analysis is as richly rewarding as it is educational. The anesthesiologist who understands the contents of this book will have deeper insight into what he is doing and what he should be doing. He will also be better informed when in the not so distant future cost-benefit and decision analysis becomes a necessary way of life for all of us.

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Malignant Hyperthermia: Current Concepts, edited by Ernest O. Henschel, 192 pp, $12.50, New York, Appleton-Century-Crofts, 1977.

Until now the single obvious difference between human and porcine malignant hyperthermia (MH) has been that susceptible pigs can trigger while awake (Porcine Stress Syndrome) while susceptible humans react only during anesthesia, and only to the potent volatile agents and the depolarizing relaxants. Now, data from D. W. Wingard imply that human awake episodes of malignant hyperthermia may simply be more subtle than those in swine, and may, in fact, be identified in retrospect as a higher rate of sudden and unexplained deaths. This chapter is valuable because these data have not been reported elsewhere. The monograph also rightly credits W. G. Locher for the recognition (and subsequent general awareness) of MH in North America. Other contributors include B. A. Britt, J. F. Ryan, C. H. Williams, and G. E. Stroble, who contributes a lucid chapter on muscle physiology and pharmacology. However, the monograph suffers generally from the weakness of a published symposium. Publication was 2 years and 11 months after the symposium took place, and the attempts to update the monograph have resulted in articles that begin as historical in format and end as awkwardly current.

Britt presents an unparalleled and impressive array of statistics on human episodes of MH, but sometimes overinterprets them. For example, her data adversely relating artificial ventilation to survival provide no information as to effectiveness of ventilation. Yet she equates artificial ventilation with hyperventilation in her discussion. (She does, in another chapter, discuss P_{CO_2} values and survival.) Another example is her probably misleading conclusion that the use of steroids significantly increases mortality. Updating in Ryan's discussion credits the successful use of dantrolene in human episodes to the 5 cases Pritt published in 1973. This is, unfortunately, 2 years before Harrison introduced dantrolene in the treatment of MH. Williams presents his own bias on the adrenergic basis of MH, a view not widely shared. The lack of any discussions prevents the reader from knowing which opinions were controversial and which were generally accepted at the symposium.

Overall, the monograph has a very narrow appeal, that being primarily for Wingard's and Britt's data.

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Facial Pain, edited by Charles C. Alling III and Parker E. Mahan, 286 pp, $22.00, Philadelphia, Lea & Febiger, 1977.

This is the 2nd edition of Dr. Alling's book, in which he this time shares the editing with Dr. Mahan. The strength of this book lies in their stressing the need for a multidisciplinary approach to the evaluation of facial pain as well as drawing authors from multiple scientific and clinical specialties. These specialties include anesthesiology, general dentistry, internal medicine, neurosurgery, oral pathology, oral surgery, orthopedic surgery, otolaryngology, pathology, pharmacology, physiology, and psychiatry.

Special attention is directed to pain mechanisms and anatomy, including neurological, musculoskeletal, vascular, and visceral-dento-cutaneous systems. Differential diagnosis of physical findings is carefully stressed throughout the book while psychodynamic aspects receive appropriate coverage. Use of nerve blocks for diagnosis and treatment is discussed not only in a separate chapter but also in other chapters where appropriate. Treatment technics comparing regional nerve blocks, surgery, radiofrequency, coagulation, stimulation technics, and use of medications are well covered.

The book discusses syndromes involving facial pain as well as separate chapters on common problems such as vascular facial pain, trigeminal neuralgia, sinus problems, and musculoskeletal pain in the face and neck. Occlusion problems, masticatory pain, and temporal mandibular joint problems are covered as are diseases of the mucosa, tongue, and salivary systems.

This book is of value to the dentist, oral surgeon, neurologist, anesthesiologist, and any other physician involved in diagnosis and treatment of head and neck pain. Not only is the material well presented, but it is also well referenced for more in-depth study.

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The Presentation of Original Work in Medicine and Biology, by Hugh Dudley, 99 pp, $6.00, New York, Churchill Livingstone, 1977.

Dudley is a surgeon in Great Britain; inevitably, perhaps, the usefulness of his book for readers in North America will be slightly limited by the 1st fact and more limited by the 2nd. Nevertheless, the basic principles for writing clear expository prose and giving concise and interesting talks are not confined by specialty or geography. These principles—well known, yet often ignored—Dudley presents lucidly and with admirable brevity.

The book includes terse chapters on deciding to communicate (direct and practical) and on the structure of scientific thought as it relates to communication in science (in places abstract and, therefore, somewhat cryptic).

Successively, these are followed by longer chapters on details of preparing manuscripts, on grammatical and syntactical strategy, and on speaking at scientific meetings. I found these 3 chapters to be excellent summaries of contemporary wisdom, pleasantly leavened by the personal opinions and practices of the author.

The book can be read in little more than an hour. Our journals and scientific meetings would benefit if all authors and speakers would devote this amount of time. Perhaps some of them will.

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* * *

Physiology, Monitoring and Therapy of the Critically Ill Patient, edited by W. C. Shoemaker and B. M. Tavares, 202 pp, $24.75, Basel, Switzerland, S. Karger AG, 1977.

This volume is based on a recent international symposium on critical care medicine. It contains 27 papers arranged under 3 headings — pathophysiology, monitoring, and therapy — representing the clinical and laboratory experiences of workers from Europe and the Americas.

The pathophysiology of "shock lung" is discussed in animals and man, and 2 other papers discuss platelet aggregation and stress ulceration. These papers pose more questions than they answer.

The section on monitoring contains 10 papers with a wide range of sophistication

and applicability. A simple technic for central venous catheterization is described, and a hand-held-computer program for routine hemodynamic calculations is given. There are papers discussing the principles and practice of currently accepted transvenous hemodynamic monitoring, and examples of the use of computers in cardiac arrhythmias, critical care, and renal disease.

Therapy is discussed in 13 papers, covering many aspects of intensive care. There are the predictable papers on mechanical ventilation, parenteral nutrition, and infections, but there are also discussions of trasylol, isosorbide dinitrate, and disopyramide, whose places in critical care medicine are being established.

There is no editorial comment in this volume, so it is not known how the papers were selected, or what impact they had at the symposium. The significant omissions in this field (if the papers on these subjects were in fact presented) are in neurological, pediatric, and renal aspects of critical care.

The volume covers reasonable ground and is likely to be of some (passing) interest to intensive therapists who are willing to exchange $24.75 for a paperback.

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Introduction to Anesthesia: The Principles of Safe Practice, by Robert D. Dripps, James E. Eckenhoff, and Leroy D. Vandam, 557 pp, $13.50, Philadelphia, W. B. Saunders Co., 1977.

For over 20 years, previous editions of Dripps, Eckenhoff, and Vandam's *Introduction to Anesthesia* have been standard texts for students of anesthesiology. The last revision was in 1972. The present, 5th edition is timely and excellent. There is no major change in format. While certain chapters have been revised only modestly, others have been revised extensively.

The chapter on respiration and respiratory care has been expanded from 14 to 36 pages. It contains new sections on mechanisms of pulmonary gas exchange and quantitative analysis of pulmonary gas exchange, both of which are well done. In addition, topics covered in earlier editions on respiratory failure and mechanical ventilation have been expanded.

Another major revision is found in the chapter on blood transfusion and IV technic, which has been changed to blood component therapy in keeping with present day practice. Indications and common problems associated with the use of whole blood and the various blood components are discussed.

New chapters include Chapter 1, "The Broad Realm of Anesthesiology," which contains a bit of history of anesthesia and a bit of the philosophy of the authors relating to the place of an anesthesiologist in anesthesia practice, the larger realm of the present-day health care system, and the medical research community.

In another new chapter, on the technics of deliberate hypotension, anesthesia for extracorporeal circulation and acupuncture have been put together. The theory, technic, intraoperative monitoring, and complications of deliberate hypotension are discussed. The background and theory of extracorporeal circulation are covered and include 2 figures depicting different oxygenators. These are followed by sections on premedication and induction of anesthesia in patients coming for cardiac surgery and an outline of extracorporeal procedure, including a table of drugs and solutions used.

Over all, it appears that the authors have again achieved their goal of "an introductory text, succinctly written, based on fact and modestly priced." They have also brought the references up to date, although in some instances it is unclear why certain ones were selected. A great strength of the book lies in the excellent selections of topics, as well as the coverage given each. It should belong to every student of anesthesia.

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Local Anesthetics, Second Edition, by Rudolph H. DeJong, 338 pp, $32.50, Springfield, Illinois, Charles C Thomas, 1977.

Local Anesthetics represents the 2nd edition of Dr. DeJong's original book, entitled *Physiology and Pharmacology of Local Anesthesia*. The strongest features of this edition remain the excellent description of the anatomy and physiology of peripheral nerves, site and mode of action of local anesthetics, Dr. DeJong's original concept of

minimal blocking concentration, and the CNS effects of local anesthetics. This section has been updated to include recent studies concerning the interaction between local anesthetics and the sodium and potassium channels in the nerve membrane.

The greatest change in the 2nd edition involves a review of the cardiovascular effects of local anesthetic drugs, a topic which was almost completely omitted from the 1st book. The cardiac electrophysiological effects of local anesthetics as related to the antiarrhythmic action of these agents, particularly lidocaine, are presented in great detail. The physiological disposition section has also been markedly expanded to include the biotransformation of clinically available local anesthetics, although information concerning the metabolism of the newest drugs, ie, bupivacaine and etidocaine, is still limited.

Some relatively minor errors are present; eg, the concentration of etidocaine in table 6-2 should be 0.25 to 1.5 percent. The main criticism concerns the adverse effects and toxicity of local anesthetics. It would have been easier for the reader if these topics were covered in the same chapter. Instead, CNS toxicity is included in the chapter on central nervous system effects, cardiovascular toxicity in the chapter on cardiovascular effects, and the final chapter, entitled "Adverse Effects," discusses mainly local tissue irritation, allergy, and complications of obstetrical regional anesthesia.

Local Anesthetics is a worthy successor to Dr. DeJong's original book. However, readers of both texts will find that it is an expanded version of the 1st book rather than a wholly new text, as described by the publisher. This book represents a valuable review of the pharmacology and toxicology of local anesthetics. Although the size (338 pages, including over 600 references) may seem rather formidable, the book is extremely easy to read. Dr. DeJong has successfully utilized an informal, almost novel-like approach, as exemplified by references to James Bond, the CIA, and the use of female figures to depict membrane receptor sites. This edition should be available as a reference text in departments of anesthesiology.

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Medicine for Anaesthetists, edited by M. D. Vickers, 571 pp, $59.50, Philadelphia, J. B. Lippincott Co., 1977.

To squeeze plungers and breathing bags, to adjust flowmeters and drip rates, or to insert needles and tubes into tissues requires no special talent. The "men" are separated from the "boys" by having acquired an intimate knowledge of disease, by relating disease to appropriate anesthetic maneuvers, and by appreciating what pharmacological or technical manipulations of function are called for (more importantly, sometimes, uncalled for).

This book is a textbook of medicine, and, although it is written for the anesthetist, it is not a textbook on anesthesia per se. Those seeking explicit instructions on how to anesthetize a patient for a specific surgical disorder or operation should look elsewhere.

Each chapter is an entity, and nearly all are written by anesthetists. Multiple authorship renders significance of illness vis-à-vis anesthesia uneven, but most sections are nicely balanced. Particularly informative chapters are those on heart, vascular, adrenal, connective-tissue, and thyroid diseases. That on diseases of the central nervous system, although well written and packed with information, bears a disappointing relationship to anesthesia. Singular treats are chapters on medical genetics relevant to anesthesia and on acute biochemical disorders, even though the former is marred by a few editorial errors.

The book is of special value to the trainee and to the anesthetist who discovers on his or her next day's schedule a patient with intercurrent disease. Older anesthetists, years beyond their intensive concern with the biochemical and physiological disarray of illness, will find the book good bedside reading. It is an expensive text; but its cost is comparable to the fee for a brief anesthetic administration, and I believe the book is worth the price.

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Persistent Pain: Modern Methods of Treatment, Volume I, edited by Sampson Lipton, 272 pp, $20.50, New York, Grune & Stratton, 1977.

This book is intended as the first of a series of 5 or 6 volumes designed to provide

a detailed and practical account of pain-relieving technics in a readable and clear way. The author hopes to prevent obsolescence by bringing out these volumes at regular intervals. This 1st volume represents a collection of individual unrelated topics on the subject of pain. The topics range from the basic neurophysiology of pain to clinical technics practiced only by the neurosurgeon, anesthesiologist, or general surgeon. The style and format of references and bibliographies were left to the discretion of the individual chapter authors. This approach has resulted in an excellent but rather wandering collection of individual chapters that might best be reviewed individually, thereby giving an overview to the content of this book.

David Bowsher's 1st chapter, on the anatomo-physiology of pain, discusses the concepts of 1st and 2nd pain and traces the anatomical ascension of the pain pathways through the various parts of the nervous system, interjecting some physiology where appropriate. This is a terse chapter, very well summarizing the basics of current thought on the neurophysiology of pain. The references are highly biased toward the English school but are adequate and current, dating up to 1976.

The 2nd chapter, by Ganz and Mullan from the University of Chicago Hospitals, covers the topic of percutaneous cordotomy from a neurosurgical viewpoint. In 13 pages the rationale, a brief history, selection of patients, and technical procedure are outlined in some detail. It represents ideal reading material for health care professionals who wish to understand the procedure in sufficient detail, to explain it to their patients, or to advise them concerning its efficacy. Unfortunately, if it is to be used for this purpose, there is little information concerning the incidence of complications. On the other hand, the chapter does not represent the type of source material one would select to study in order to perform the procedure. It is unfortunate that this otherwise excellent chapter was not directed toward a specific audience, such as primary care physicians or pain specialists who might wish to advise their patients in some detail concerning the possible outcomes of such a procedure.

Headache and pain in the neck are covered in 1 comprehensive chapter, which suffers from covering too much ground too lightly. The approach to headaches, tension headaches, vascular headaches, the more serious pathological states of cerebral aneurysms, tumors, and raised intercranial pressure, and the neuralgias of the glossopharyngeal and trigeminal nerve are covered. If this were not enough, central pain states such as thalamic syndrome and atypical facial pain, classified here as depressive facial pain, are covered together with carcinoma of the nasopharynx, diabetic cranial nerve palsies, Costen's syndrome, and giant cell arteritis. The chapter ends with referred pain from cervical spondylosis. This represents a very ambitious attempt to cover the total material related to pain in the head and neck. But the material alone requires a whole book and not just a 25-page chapter. The references are adequate, with a reading list included.

The chapter on spinal (intrathecal) and extradural analgesia by Maher and Mehta is one of the most valuable and informative in this book. The subject is extremely well organized; indications, technic, and complications are discussed both for subarachnoid and extradural analgesia technics. The chapter is heavily and appropriately referenced and recommendations specifically given for avoiding some of the common complications. It is obvious to one practiced in these technics that the authors speak from practical experience with a great many cases and in-depth knowledge of the literature. This chapter alone makes the purchase of this book worthwhile.

A brief, skillfully written chapter by Felix Mann on acupuncture is informative in discussing its history, experimental background, and current practice. It is obviously intended to be informative and not a "how to do it manual" and achieves this goal directly and clearly.

The psychiatric management of patients with chronic pain is concisely surveyed by Dr. Merskey. He includes many areas of psychiatry peculiar to the chronic pain patient, such as management of analgesia medication with the aid of psychotropic drugs and the role of depression in chronic pain. This is an informative chapter that is unfortunately all too brief.

The chapter entitled "Surgery for the Relief of Pain" catalogs the various neurosurgical approaches to the ascending tracts carrying pain impulses and in addition discusses application of electrical stimulation to these same areas. This is a brief but good

review chapter that might be a useful information source for someone outside the field of chronic pain or neurosurgery. It is an adequately and excellently referenced chapter.

Morricca's chapter on pituitary neuroadenolysis is a description of the development of this technic and its use in the management of cancer pain. This as yet little used technic does show some promise, and this chapter does an excellent job of explaining the procedure, discussing its mechanism of action, and giving some of the results obtained.

The excellent and well-organized chapter by Mumford on dental, oral, and facial pain is necessary reading for every health care professional who lacks dental training. Here dental pain is nicely classified into dentinal, pulpal, periapical, periodontal, and iatrogenic pain. In addition, pain within the bone is discussed, including that from abscess, osteomyelitis, sinusitis, and cyst. Multiple other causes of hard-tissue pain are noted, and soft-tissue lesions from gingival disease to glandular disease are discussed. Masticatory disturbances are included as a pain source. The chapter is clear and concise and has a reading list that is appropriate for the pain specialist. This is another chapter that makes the purchase of the text worthwhile.

The chapter "Peripheral Nerve Blocking in the Relief of Pain," by Mark Swerdlow, is an excellent exposé of currently available technics, their indications for use, and the cautions required in their application. Some instructions are given for specific blocks but the chapter's primary interest is informing the non-nerve-block expert of the available technics, the rationale concerned with their application, and the results that might be expected.

The concluding chapter on drug therapy discusses many of the different types of drugs and their actions that might be used in the management of pain. Inflammatory vasoactive drugs and those affecting neural transmission are discussed as well as the use of narcotic analgesics. The chapter is complicated by the use of many British trade names in addition to the usual generic names. The action of anticonvulsant drugs such as Tegretol® on central pain states such as trigeminal neuralgia is explained by suggesting that they reduce synaptic transmission of the pain impulse. The reference and reading list for this chapter are adequate.

The editor and publishers of this 1st volume of a proposed continuing series are to be commended for their effort in attempting this much needed task. Unfortunately, much of the work contained in this volume lacks depth or is available elsewhere. However, the outstanding chapters mentioned do make this book a worthwhile acquisition as a convenient reference source.

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Scientific Articles: March-April, 1978

VENOUS AIR EMBOLISM: COMPARATIVE MERITS OF EXTERNAL CARDIAC MASSAGE, INTRACARDIAC ASPIRATION, AND LEFT LATERAL DECUBITUS POSITION—Simeon B. Alvaran, MD, Juey Kong Toung, MD, Thomas E. Graff, MD, and Donald W. Benson, MD, Baltimore, Maryland

N_2O EXPOSURE IN THE OPERATING ROOM—Froukje M. Beynen, MD, Thomas J. Knopp, BA, and Kai Rehder, MD, Rochester, Minnesota

LOWER ESOPHAGEAL SPHINCTER TONE DURING REVERSAL OF NEUROMUSCULAR BLOCKADE BY ATROPINE AND NEOSTIGMINE—J.G. Brock-Utne, FFA, J.W. Downing, FFARCS, S. Welman, MB, G.E. Dimopoulos, FRCS, and M.G. Moshal, MRCP, Durban, South Africa

EEG ABNORMALITIES FOLLOWING HALOTHANE ANESTHESIA—Kim J. Burchiel, MD, James J. Stockard, MD, PhD, Roderick K. Calverley, MD, N.Ty Smith, MD, Mary L. Scholl, MD, and Richard I. Mazze, MD, San Francisco, California

AN INFANT CIRCUIT WITH A WATER VAPORIZER WARMED BY CARBON DIOXIDE NEUTRALIZATION—Jack Chalon, MD, Ronald Simon, Chandrakant Patel, MD, Sivam Ramanathan, MD, Steven Sessler, BS, and Herman Turndorf, MD, New York, New York

COMPARISON OF ANESTHETIC SOLUTIONS USED IN LUMBAR AND CAUDAL PERIDURAL ANESTHESIA—A. Galindo, MD, PhD, Miami, Florida, O. Benavides, MD, S. Ortega de Munos, MD, O. Bonilla, MD, and R. Pena, MD, Bogota, Colombia

PHYSOSTIGMINE AND ANESTHETIC REQUIREMENT FOR HALOTHANE IN DOGS—Richard W. Horrigan, MD, San Francisco, California

ANESTHESIA FOR TRANSSPHENOIDAL SURGERY OF THE HYPOPHYSEAL REGION—Joseph M. Messick, Jr., MD, Edward R. Laws, Jr., MD, and Charles F. Abboud, MD, Rochester, Minnesota

INCREASE IN ANESTHETIC UPTAKE, EXCRETION, AND BLOOD SOLUBILITY IN MAN AFTER EATING—Edwin S. Munson, MD, Edmond I. Eger II, MD, Min K. Tham, PhD, and William J. Embro, BS, Gainesville, Florida

CARDIAC DYSRHYTHMIAS FOLLOWING REVERSAL OF NEUROMUSCULAR BLOCKING AGENTS IN GERIATRIC PATIENTS —William D. Owens, MD, Lawrence S. Waldbaum, MD, and C.R. Stephen, MD, St. Louis, Missouri

GAS EMBOLISM DEATH AFTER LAPAROSCOPY DELAYED BY "TRAPPING" IN PORTAL CIRCULATION—Benjamin Root, MD, Matthew N. Levy, MD, Stanley Pollack, MD, Mortimer Lubert, MD, and Kalindi Pathak, MD, Cleveland, Ohio

PREVALENCE AND SURVIVAL OF MICROBIAL CONTAMINANTS IN HEATED NEBULIZERS—Moniek S. Spaepen, R. Pharm, James R. Berryman, RRT, Hollis A. Bodman, MS, Ruth B. Kundsin, ScD, and Vladimir Fencl, MD, Boston, Massachusetts

CLINICAL REPORTS

ANESTHETIC MANAGEMENT OF EMERGENCY CESAREAN SECTION IN A PATIENT WITH EPIDERMOLYSIS BULLOSA DYSTROPHICA POLYDYSPLASTICA—Richard E. Berryhill, MD, Jonathan L. Benumof, MD, Lawrence J. Saidman, MD, Penelope C. Smith, MD, and Michael H. Plumer, MD, San Diego, California

ANESTHETIC MANAGEMENT OF COMBINED CESAREAN SECTION AND EXCISION OF PHEOCHROMOCYTOMA—George E. Burgess, III, MD, John R. Cooper, MD, Robert J. Marino, MD, and Martin J. Peuler, MD, New Orleans, Louisiana

SEVERE HYPERTENSION ASSOCIATED WITH PANCURONIUM BROMIDE—Donald S. Fraley, MD, Gary L. Lemoncelli, MD, and Arnett Coleman, MD, Pittsburgh, Pennsylvania

A METHOD OF BLOOD CONSERVATION IN JEHOVAH'S WITNESSES: INCIRCULATION DIVERSION AND REFUSION—Henry H. Khine, MD, Ramarao Naidu, MD, Henry Cowell, MD, and G. Dean MacEwen, MD, Wilmington, Delaware

BLOOD CLOT FORMATION DURING MULTIPLE CARDIOPULMONARY BYPASS PROCEDURES NECESSITATED BY MASSIVE HEMORRHAGE—Delf O. King, MD, and Peter B. Kane, MD, Syracuse, New York

RECALL FOLLOWING KETAMINE ANESTHESIA FOR OPEN HEART SURGERY: REPORT OF A CASE—Surendra M. Kumar, MD, Sujit K. Pandit, MD, and Peter F. Jackson, MD, Ann Arbor, Michigan

WATER-INDUCED RESISTANCE IN DISPOSABLE RESPIRATORY CIRCUIT BACTERIA FILTERS—Edward A. Loeser, MD, Salt Lake City, Utah

MALIGNANT HYPERTHERMIA IN A SIX-MONTH OLD INFANT: A CASE REPORT—James F. Mayhew, LCDR MC USN, Joseph Rudolph, LT MC USNR, and Raymond E. Tobey, CAPT MC USN, Bethesda, Maryland

SUCCESSFUL EPIDURAL ANESTHESIA FOLLOWING EPIDURAL BLOOD PATCH—John S. Naulty, MD, LCDR MC USNR, and Robert Herold, MD, LT MC USNR, Bethesda, Maryland

TWO HAZARDS OF GAS SCAVENGING—Mehrdad Tavakoli, MD, and Alfred Habeeb, MD, Birmingham, Alabama

A Guide for Authors

Manuscripts should be sent to:

Nicholas M. Greene, M.D.
Editor in Chief, *Anesthesia and Analgesia . . . Current Researches*
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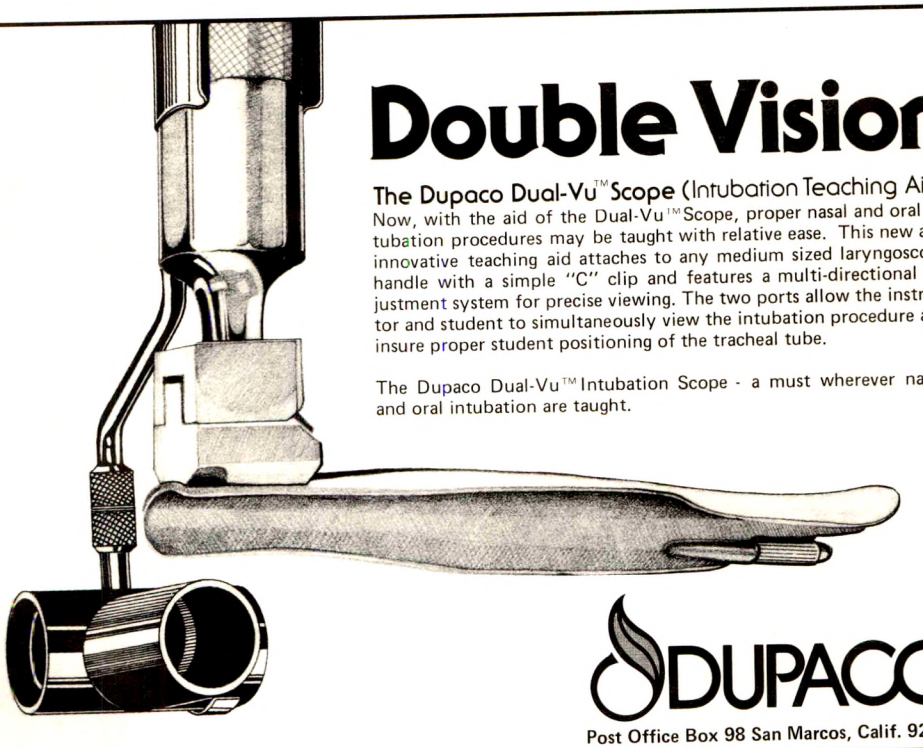
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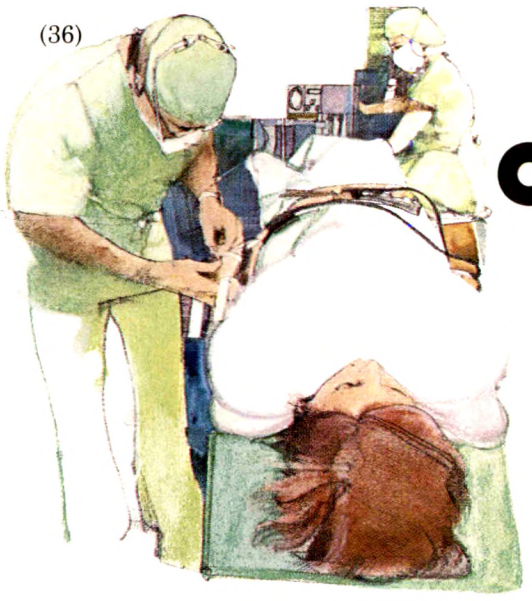


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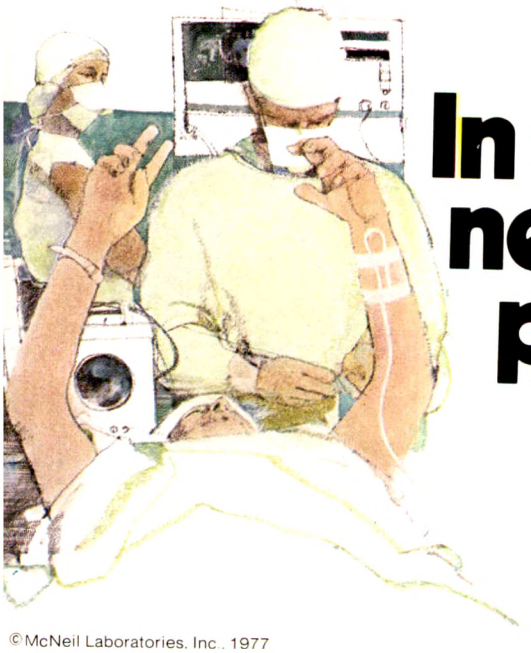
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– for administration with a neuroleptic such as *INAPSINE®* (droperidol) injection as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia.

CONTRAINDICATIONS SUBLIMAZE (fentanyl) is contraindicated in patients with known intolerance to the drug.

WARNINGS AS WITH OTHER CNS DEPRESSANTS, PATIENTS WHO HAVE RECEIVED SUBLIMAZE (fentanyl) SHOULD HAVE APPROPRIATE SURVEILLANCE.

RESUSCITATIVE EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

See also discussion of narcotic antagonists in Precautions and Overdosage.

If SUBLIMAZE (fentanyl) is administered with a tranquilizer such as *INAPSINE* (droperidol), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used *fluids and other countermeasures to manage hypotension should be available.*

As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE (fentanyl) persists longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as 1/4 to 1/3 those usually recommended. SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. The effect is related to the speed of injection and its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

Drug Dependence – SUBLIMAZE (fentanyl) can produce drug dependence of the morphine type and therefore has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE (fentanyl) in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure – SUBLIMAZE (fentanyl) should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition, SUBLIMAZE (fentanyl) may obscure the clinical course of patients with head injury.

Usage in Children – The safety of SUBLIMAZE (fentanyl) in children younger than two years of age has not been established.

Usage in Pregnancy – The safe use of SUBLIMAZE (fentanyl) has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

PRECAUTIONS *The initial dose of SUBLIMAZE (fentanyl) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses.*

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms (see Actions) SUBLIMAZE (fentanyl) can also alter respiration. Therefore, when SUBLIMAZE (fentanyl) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia. When used with a tranquilizer such as *INAPSINE* (droperidol), blood pressure may be altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE (fentanyl) should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory rese and others with potentially compromised respiration. In such patients, narcc may additionally decrease respiratory drive and increase airway resistar During anesthesia, this can be managed by assisted or controlled respirat Respiratory depression caused by narcotic analgesics can be reversed narcotic antagonists. Appropriate surveillance should be maintained beca the duration of respiratory depression of doses of fentanyl employed dur anesthesia may be longer than the duration of the narcotic antagonist act Consult individual prescribing information (levallorphan, nalorphine a naloxone) before employing narcotic antagonists.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMA (fentanyl), pulmonary arterial pressure may be decreased. This fact should considered by those who conduct diagnostic and surgical procedures wh interpretation of pulmonary arterial pressure measurements might determ final management of the patient.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, a general anesthetics) will have additive or potentiating effects with SUBLIMA (fentanyl). When patients have received such drugs, the dose of SUBLIMA (fentanyl) required will be less than usual. Likewise, following the adminis tion of SUBLIMAZE (fentanyl), the dose of other CNS depressant drugs sho be reduced.

SUBLIMAZE (fentanyl) should be administered with caution to patients with l and kidney dysfunction because of the importance of these organs in metabolism and excretion of drugs.

SUBLIMAZE (fentanyl) may produce bradycardia, which may be treated v atropine; however, SUBLIMAZE (fentanyl) should be used with caution in tients with cardiac bradyarrhythmias.

When SUBLIMAZE (fentanyl) is used with a tranquilizer such as *INAPSI* (droperidol), hypotension can occur. If this occurs, the possibility hypovolemia should also be considered and managed with appropriate par teral fluid therapy. Repositioning the patient to improve venous return to heart should be considered when operative conditions permit. Care should exercised in moving and positioning of patients because of the possibility orthostatic hypotension. If volume expansion with fluids plus other counterm sures do not correct hypotension, the administration of pressor agents otl than epinephrine should be considered. Because of the alpha-adrener blocking action of *INAPSINE* (droperidol), epinephrine may paradoxically crease the blood pressure in patients treated with *INAPSINE* (droperidol).

When *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) and the EEC used for postoperative monitoring, it may be found that the EEG pattern retur to normal slowly.

ADVERSE REACTIONS As with other narcotic analgesics, the most comm serious adverse reactions reported to occur with SUBLIMAZE (fentanyl) a respiratory depression, apnea, muscular rigidity, and bradycardia; if the remain untreated, respiratory arrest, circulatory depression or cardiac arr could occur.

Other adverse reactions that have been reported are hypotension, dizzine blurred vision, nausea, emesis, laryngospasm, and diaphoresis.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMA (fentanyl), the following adverse reactions can occur: chills and/or shiverir restlessness, and postoperative hallucinatory episodes (sometimes associat with transient periods of mental depression); extrapyramidal symptoms (d tonia, akathisia, and oculogyric crisis) have been observed up to 24 ho postoperatively. When they occur, extrapyramidal symptoms can usually controlled with anti-Parkinson agents. Postoperative drowsiness is also f quently reported following the use of *INAPSINE* (droperidol).

Elevated blood pressure, with and without pre-existing hypertension, has be reported following administration of SUBLIMAZE (fentanyl) combined with *APSINE* (droperidol). This might be due to unexplained alterations in symp thetic activity following large doses; however, it is also frequently attributed anesthetic and surgical stimulation during light anesthesia.

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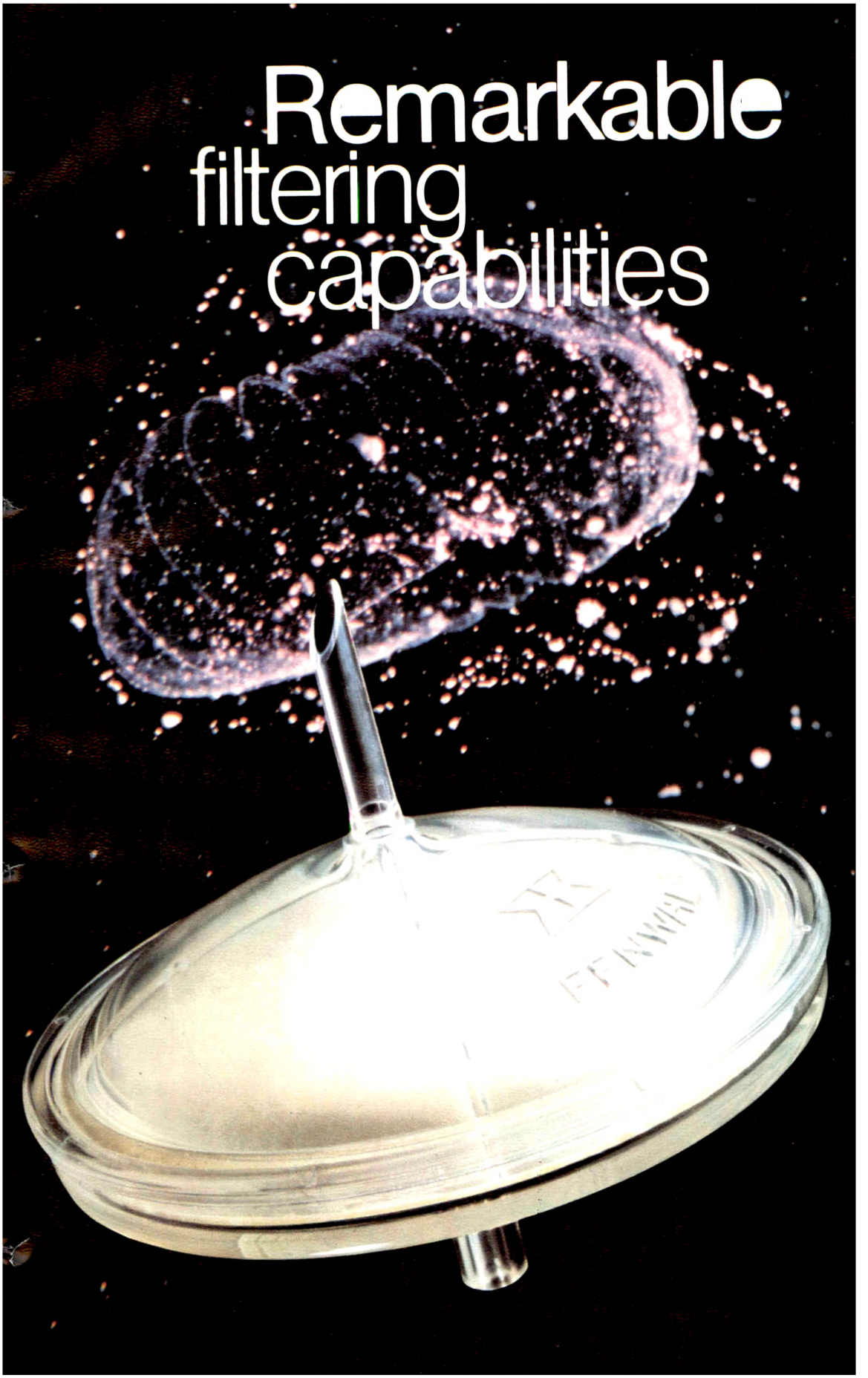
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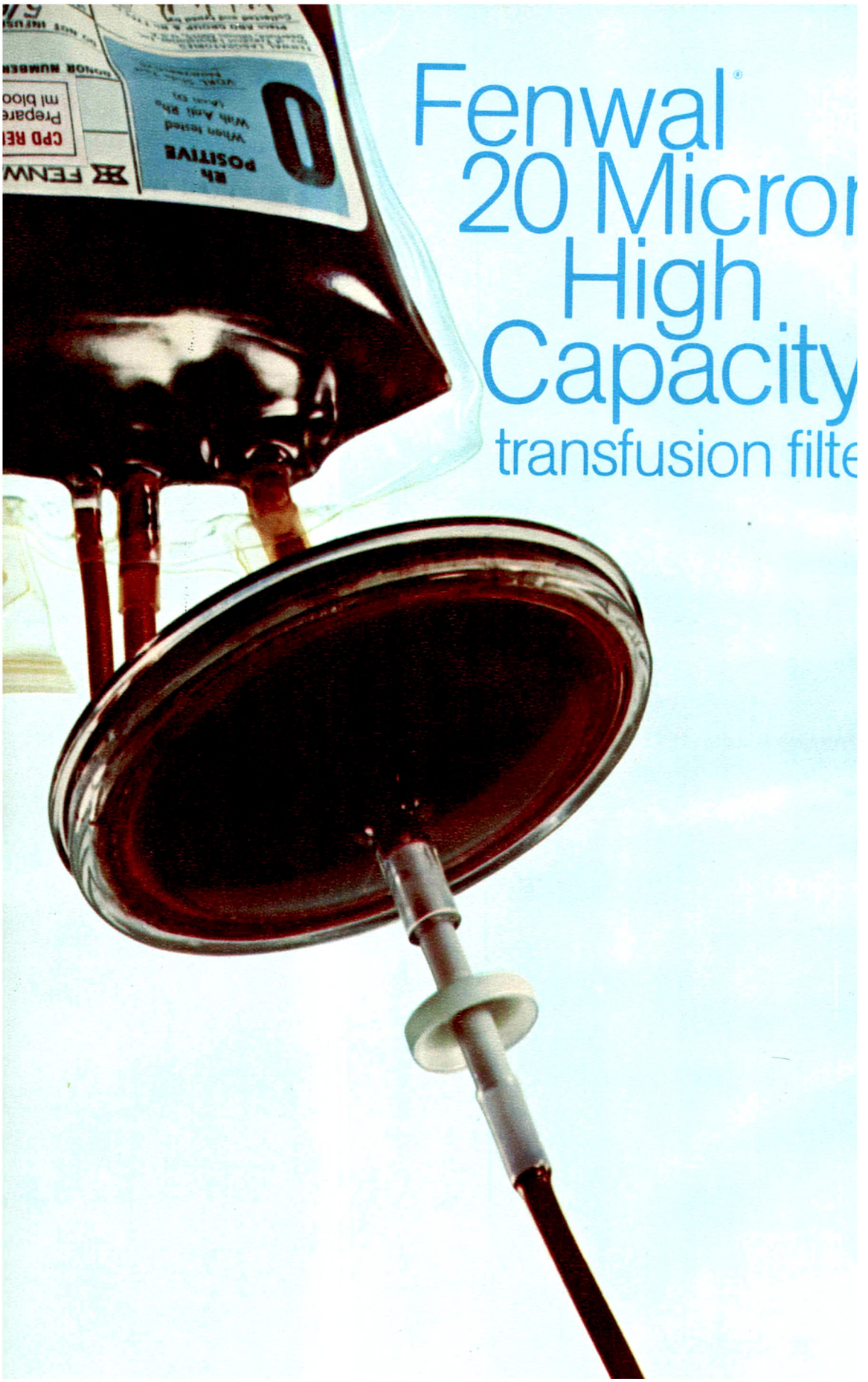
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Fig. A. **Before filtration**
60x magnification of 20μm screen having filtered 21-day CPD whole blood.

Fig. B. 1800x detail of microaggregates and debris depicted in Fig. A.

Fig. C. **After filtration**
60x magnification of 20μm screen having filtered 21-day CPD whole blood that had been filtered first with the Fenwal 20 Micron High Capacity Filter.

Fig. A.

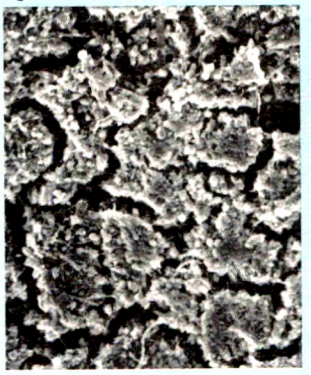


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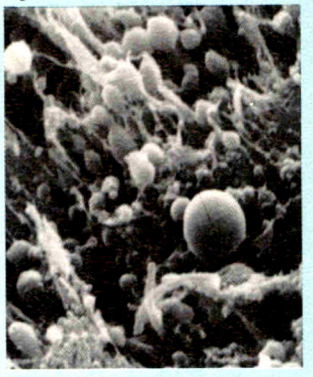
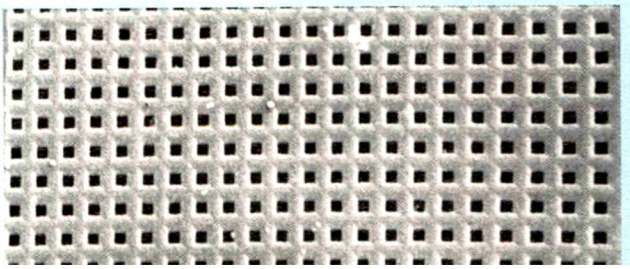
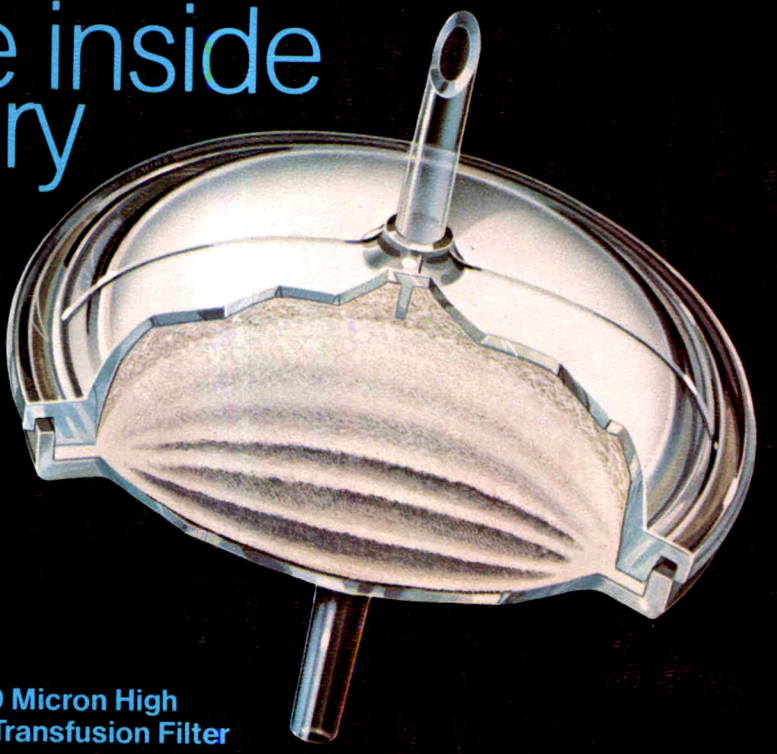


Fig. C.

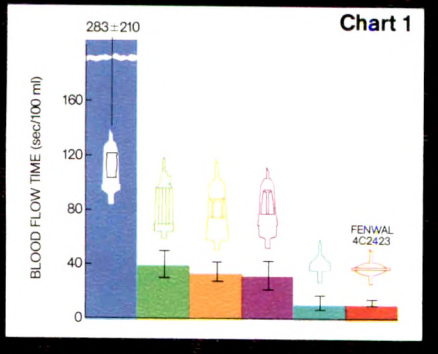


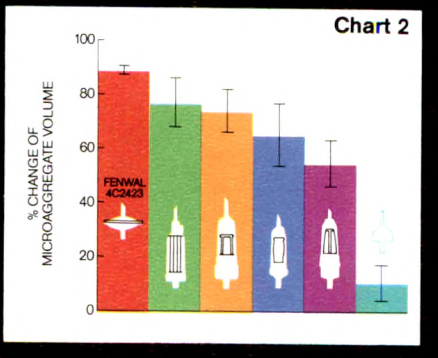
the inside story



Fenwal 20 Micron High Capacity Transfusion Filter

The six-layer, large surface area, graduated density design of the Fenwal 20 Micron High Capacity Transfusion Filter presents countless pathways through which blood may flow. Exceptionally rapid flow rates are possible as this multiplicity of paths offers minimal resistance to blood flow. The large surface area provides extended filtering capacity for multiple unit blood transfusion. The graduated density principle results in uniform collec of debris throughout the filter media. Microaggrega are trapped in the open upper layer, while the dense bottom layers efficiently remove microaggregates o to 20 microns in diameter.





Combining Rapid Flow Rate and Remarkable Filtering Efficiency

These charts are derived from an independent laboratory study.[1] filters studied were commercially available. The tests employed i the study are compatible with accepted techniques and duplicat earlier published report.[2]

Chart 1. **Blood Flow Time**
Time required to filter 100 ml of 21-day CPD whole blood.

Chart 2. **% Change of Microaggregate Volume**
Indicates filter's efficiency in removing microdebris down 10-80 micron range.

Code 4C2423

20 MICRON HIGH CAPACITY TRANSFUSION FILTER for removal microaggregates from whole blood or red blood cells. Multiple un may be administered through this filter. Packaged 1 unit per box, 24 boxes per case.

Read directions provided with this product before using. Observe notes and cautions.

Caution: Federal (U.S.A.) law restricts this device to sale by or on order of a physician.

References
1. Marshall, B.E., Wurzel, H.A., Ewing, B., et al. Evaluation of Fenwal 4C2423 Transfusion Filter. Submitted for publication, 1976.
2. Marshall, B.E., Wurzel, H.A., Ellison, N., et al. Microaggregate formation in stored blood. Comparison of Bentley, Fenwal, Pall, and Swank. Circ. Shock 2:4, 249-63, 19

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...INSTANT ATOMIZATION FOR FAST TOPICAL ANESTHESIA

Fast, measured topical anesthesia is ready at your finger tips in a Rals Power Unit. Forget about pumping bulbs, uneven atomization, and limited spraying duration. The Rals Power Unit uses a non-toxic propellant, dichlorodifluoromethane (freon) to activate standard DeVilbiss Atomizers No's. 151, 152 and 163. Instantly, a fine mistlike spray is produced. A graduated solution vial is available for measuring the amount of solution administered.

The Rals Power Unit has been proven effective in cocainization prior to endotracheal intubation, endoscopic instrumentation, laryngotracheal insufflation, and in a variety of nose and throat procedures.

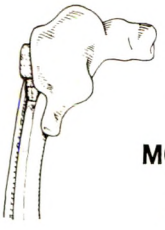
Rals Power Unit #168 are supplied six to a box with adaptor top and metal base. Illustration shows #152 atomizer. All styles in stock.

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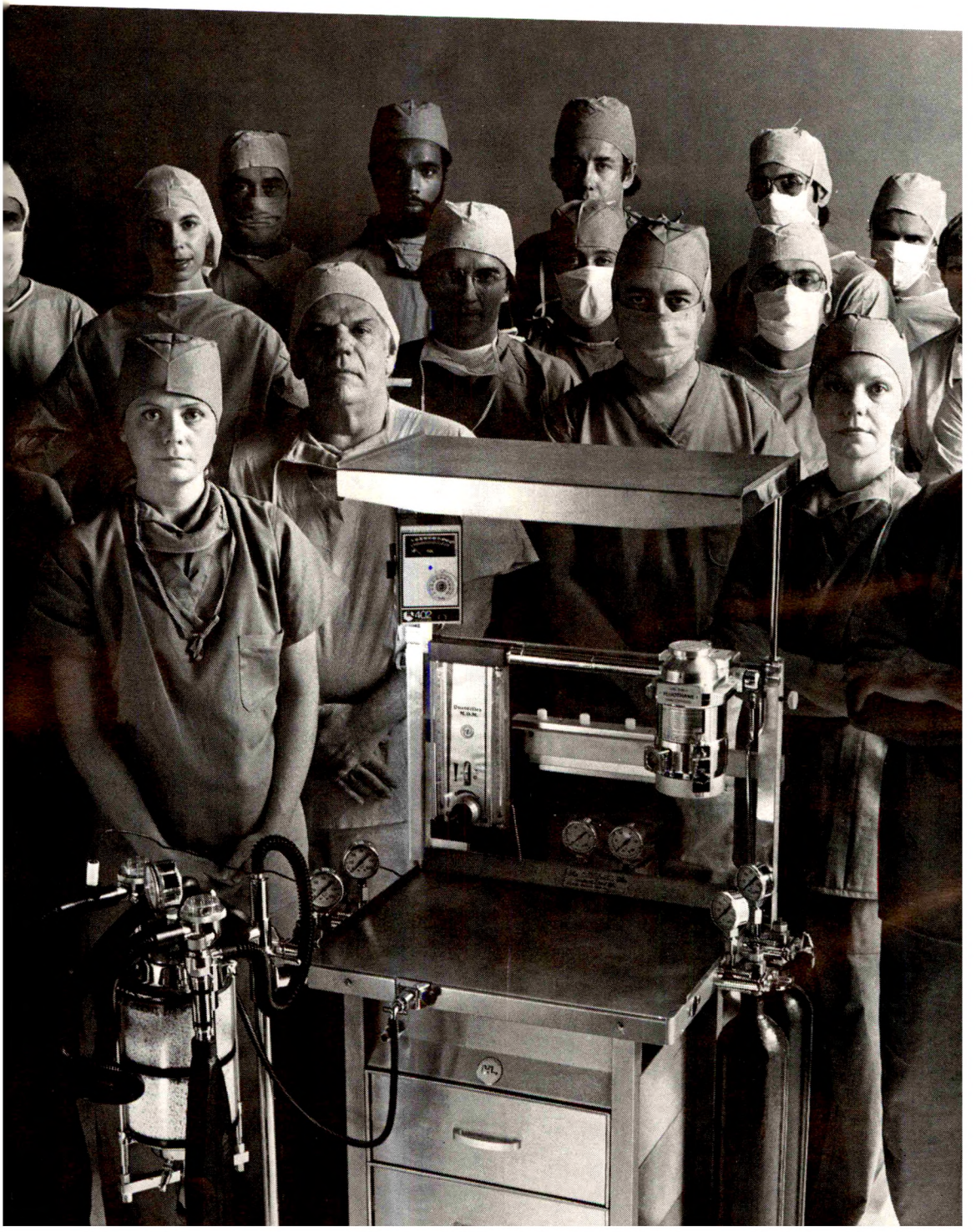
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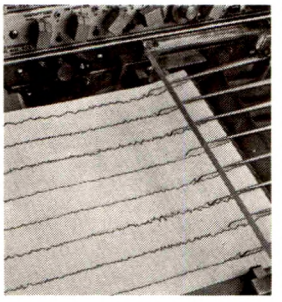
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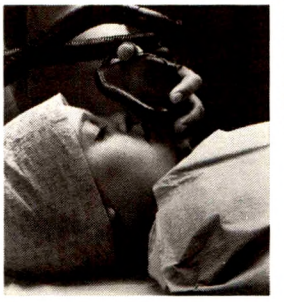
More anesthesiologist choose it more often...



for good reasons

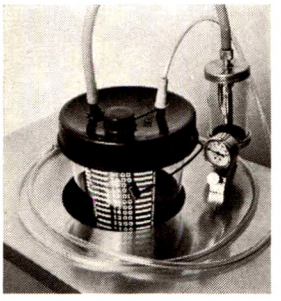
EEG patterns indicative of cortical seizure activity which may be associated with clonic-tonic muscle activity have not been reported with the use of FLUOTHANE (halothane, U.S.P.)

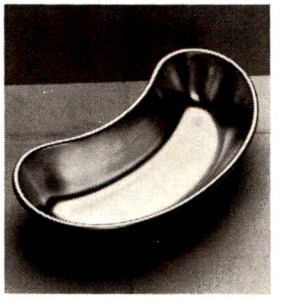




Rapid, smooth induction—particularly important in pediatric surgery—is facilitated by the pleasant odor of FLUOTHANE.

No increase in salivary or bronchial secretions is produced with FLUOTHANE.





Emergence is rapid and tranquil, with minimal nausea and vomiting* ...adjustment in the depth of anesthesia with FLUOTHANE is simple.

FLUOTHANE®
(halothane, U.S.P.)

the most widely used inhalation anesthetic in the world... over 110 million administrations in the U.S. alone

Ayerst®

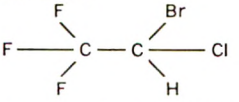
*See following page for full prescribing information.

for a variety of procedures, for a lot of good reasons

FLUOTHANE® (halothane, U.S.P.) the most widely used inhalation anesthetic in the world

(Complete text of package circular.)

Description. FLUOTHANE, brand of halothane, U.S.P., is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:



The specific gravity is 1.872-1.877 at 20° C, and the boiling point (range) is 49° C-51° C at 760 mm Hg. The vapor pressure is 243 mm Hg at 20° C. The blood/gas coefficient is 2.5 at 37° C, and the olive oil/water coefficient is 220 at 37° C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane, U.S.P.) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all the diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE (halothane, U.S.P.) is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy. Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane, U.S.P.) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

Adverse Reactions. The following adverse reactions have been reported: hepatic necrosis, cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide.

How Supplied. No. 3125—Unit packages of 125 ml and 250 ml of halothane U.S.P. stabilized with 0.01% thymol (w/v

773

Ayerst® Ayerst Laboratories
New York, N.Y. 10017

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in selected cases of shock

24mg/ml

INJECTION

DECADRON® PHOSPHATE

(DEXAMETHASONE SODIUM PHOSPHATE | MSD)

Contraindications: Systemic fungal infections (See **Warnings** re amphotericin B); hypersensitivity to any component.

Warnings: Corticosteroids may exacerbate systemic fungal infections and should not be used in presence of such infections unless needed to control reactions to amphotericin B; there have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive failure. In patients subjected to unusual stress, increase dosage of rapidly acting corticosteroids before, during, and after the stressful situation. Corticosteroids may mask some signs of infection; new infections, decreased resistance, and inability to localize infection may occur. Moreover, corticosteroids may affect the nitroblue-tetrazolium test for bacterial infection and produce false negative results. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and glaucoma with possible damage to optic nerves and may enhance the establishment of secondary, fungal or viral ocular infections.

Usage in pregnancy: In pregnancy or women of childbearing potential, weigh anticipated benefits against possible hazards to mother and embryo or fetus. Infants of mothers on substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism. Corticosteroids appear in breast milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects; mothers taking pharmacologic doses of corticosteroids should be advised not to nurse.

Elevation of blood pressure, salt and water retention, and increased excretion of potassium may occur with large doses of synthetic corticosteroids; dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion. Patients on corticosteroids should not be vaccinated against smallpox and other immunization procedures should not be undertaken except in those receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

In active tuberculosis, use should be restricted to fulminating or disseminated tuberculosis and should be in conjunction with appropriate antituberculous regimen; in latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur, and patients should receive chemoprophylaxis during prolonged corticosteroid therapy.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to parenteral administration, especially in patients with history of drug allergy.

Precautions: This steroid is sensitive to heat and should not be autoclaved. Drug-induced secondary adrenocortical insufficiency, which may be minimized by gradual reduction of dosage, may persist for months after discontinuation of therapy. In any situation of stress occurring during that period, hormone therapy should be reinstituted. If patient already is receiving steroids, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or mineralocorticoid should be administered concurrently.

In hypothyroidism and in cirrhosis, there is an enhanced effect of corticosteroids. Use cautiously in patients with ocular herpes simplex for fear of corneal perforation.

The lowest possible dose should be used, and when reduction in dosage is possible, it must be gradual. Psychic derangements may appear, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations, and existing emotional instability or psychotic tendencies may be aggravated. Psychological and/or physiological dependency may develop with long-term use; withdrawal symptoms include anorexia, vague pains, weakness, and lethargy. In hypoprothrombinemia, use aspirin cautiously in conjunction with corticosteroids.

Use with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection; also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Fat embolism has been reported as a possible complication of hypercortisonism. When large corticosteroid doses are given, some authorities advise that antacids be administered between meals to help to prevent peptic ulcer.

Growth and development of infants and children on prolonged therapy should be carefully followed. Motility and number of spermatozoa may be increased or decreased. Phenytoin, phenobarbital, ephedrine, and rifampin may enhance the metabolic clearance of corticosteroids, resulting in decreased blood levels and lessened physiologic activity, thus requiring adjustment in corticosteroid dosage; these interactions may interfere with dexamethasone suppression tests which should be interpreted with caution during administration of these drugs. Prothrombin time should be checked frequently in patients receiving concomitant coumarin anticoagulants because of reports that corticosteroids have altered the response to these anticoagulants; studies have shown the usual effect to be inhibition of response to coumarins, although there have been some reports of potentiation. When corticosteroids are administered concomitantly with potassium-depleting diuretics, patients should be observed closely for development of hypokalemia.

Intra-articular injection may produce systemic as well as local effects. Appropriate examination of any joint fluid present is necessary to exclude a septic process. Marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise is suggestive of septic arthritis. If this complication occurs and diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted. Injection of a steroid into an infected site is to be avoided. Corticosteroids should not be injected into unstable joints. Patients should be impressed strongly with the importance of not overusing joints in which symptomatic benefit has been obtained as long as the inflammatory process remains active. Frequent intra-articular injection may result in damage to joint tissues. The slower rate of absorption following intramuscular administration should be recognized.

Adverse Reactions: *Fluid and electrolyte disturbances*—Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal*—Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal*—Peptic ulcer with possible subsequent perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic*—Impaired wound healing; thin fragile skin; petechiae and ecchymoses; erythema; increased sweating; may suppress reactions to skin tests; burning or tingling, especially in the perineal area (after IV injection); other cutaneous reactions, such as allergic dermatitis, urticaria, angioneurotic edema. *Neurologic*—Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache. *Endocrine*—Menstrual irregularities; development of cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic*—Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic*—Negative nitrogen balance due to protein catabolism. *Other*—Anaphylactoid or hypersensitivity reactions; thromboembolism; weight gain; increased appetite; nausea; malaise; psychological and/or physiologic dependency. *Additional* adverse reactions related to parenteral corticosteroid therapy: Rare instances of blindness associated with intralesional therapy around the face and head; hyperpigmentation or hypopigmentation; subcutaneous and cutaneous atrophy; sterile abscess; postinjection flare (following intra-articular use); Charcot-like arthropathy.

Note: Injection, 4 mg/ml — *For intravenous, intramuscular, intra-articular, intralesional, and soft-tissue injection.* Injection, 24 mg/ml — *For intravenous injection only. DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE AND THE RESPONSE OF THE PATIENT.*

How Supplied: Injection in two concentrations: Injection, 4 mg/ml, in 1-ml disposable syringes and 1-ml, 5-ml, and 25-ml vials, containing per ml: dexamethasone sodium phosphate equivalent to 4 mg dexamethasone phosphate or 3.33 mg dexamethasone; Inactive ingredients per ml: 8 mg creatinine, 10 mg sodium citrate, sodium hydroxide to adjust pH, water for injection q.s., with 1 mg sodium bisulfite, 1.5 mg methylparaben, and 0.2 mg propylparaben added as preservatives; Injection, 24 mg/ml, in 5-ml and 10-ml vials, containing per ml: dexamethasone sodium phosphate equivalent to 24 mg dexamethasone phosphate or 20 mg dexamethasone; Inactive ingredients per ml: 8 mg creatinine, 10 mg sodium citrate, 0.5 mg disodium edetate, sodium hydroxide to adjust pH, water for injection q.s., with 1 mg sodium bisulfite, 1.5 mg methylparaben, and 0.2 mg propylparaben added as preservatives.

For more detailed information, consult your MSD representative or see full prescribing information.

Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

J6D102R2 (114)

MSD

MERCK SHARP DOHME

in shock

unresponsive to conventional therapy
if adrenocortical insufficiency is suspected

24 mg/ml

INJECTION

DECADRON® PHOSPHATE
(DEXAMETHASONE SODIUM PHOSPHATE | MSD)

high potency • low volume





240 mg – 10-ml vial
equivalent to 1000 mg
methylprednisolone

120 mg – 5-ml vial
equivalent to 500 mg
methylprednisolone

For IV use only. Easily identified as the high-potency concentration of Injection DECADRON® Phosphate – look for the red band on the carton and vial.

MSD
MERCK SHARP

ANTILIRIUM

(Physostigmine Salicylate)

TO REVERSE THE TOXIC EFFECTS UPON THE CENTRAL NERVOUS SYSTEM CAUSED BY DRUGS IN CLINICAL OR TOXIC DOSAGES CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING.

DRUGS AND CHEMICALS CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING:

- AMITRIPTYLINE (Elavil, Triavil, Etrafon)
- ANISOTROPINE METHYLBROMIDE
- ATROPINE
- BELLADONNA
- BENACTYZINE
- CHLORPHENIRAMINE
- CYCLOPENTOLATE
- DESIPRAMINE (Norpramin, Pertofrane)
- DICYCLOMINE
- DIPHENHYDRAMINE
- DOXEPIN (Sinequan)
- HOMATROPINE
- HYOSCINE
- HYOSCYAMUS
- IMIPRAMINE (Tofranil, Presamine)
- ISOPROPAMIDE
- MEPENZOLATE
- METHANTHELINE
- METHAPYRILENE
- NORTRIPTYLINE (Aventyl)
- PIPENZOLATE BROMIDE (Piptal)
- PROPANTHELINE
- PROTRIPTYLINE (Vivactil)
- PYRILAMINE
- SCOPOLAMINE
- STRAMONIUM
- PHENOTHIAZINES
- TRICYCLIC ANTIDEPRESSANTS (Aventyl, Elavil, Etrafon, Norpramin, Pertofrane, Presamine, Tofranil, Triavil, Vivactil)
- THIORIDAZINE (Mellaril)

INDICATIONS: TO REVERSE THE TOXIC EFFECTS UPON THE CENTRAL NERVOUS SYSTEM CAUSED BY DRUGS IN CLINICAL OR TOXIC DOSAGES CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING.

SEVERE ANTICHOLINERGIC POISONING MAY PRODUCE: COMA, MEDULLARY PARALYSIS AND DEATH.

CENTRAL TOXIC EFFECTS MAY INCLUDE: HALLUCINATIONS, DELIRIUM, DISORIENTATION, ANXIETY AND HYPERACTIVITY.

Before prescribing, please consult complete product information, a summary of which follows:

ACTION: ANTILIRIUM (physostigmine salicylate) is a salicylic acid derivative of an alkaloid extracted from seeds of Physostigma Venenosum (calabar bean). The action of the parasympathetic nerves is intermediated by the formation of acetylcholine at the peripheral end of these nerves. Physostigmine inhibits the destructive action of cholinesterase and thereby prolongs and exaggerates the effect of the acetylcholine.

Physostigmine contains a tertiary amine and easily crosses the blood brain barrier, while neostigmine contains a quaternary amine and is not capable of crossing the structure. This may explain why neostigmine does not cause reversal of anticholinergic-induced delirium while physostigmine does.

Dramatic reversal within minutes of coma, hallucinations, and other signs can be expected if the diagnosis is correct and the patient has not suffered anoxia or other insult. Therapeutic doses may be necessary at intervals as life-threatening signs recur. Physostigmine is destroyed in the body in 60 to 120 minutes.

CONTRAINDICATIONS: Physostigmine should not be used in the presence of asthma, gangrene, diabetes, cardiovascular disease, mechanical obstruction of the intestines or urogenital tract or any vagotonic state, and in patients receiving choline esters or depolarizing neuromuscular blocking agents.

WARNING: If excessive symptoms of salivation, emesis, urination and defecation occur, the use of ANTILIRIUM should be terminated. If excessive sweating or nausea occur, the dosage should be reduced.

Intravenous administration should be at a slow, controlled rate, no more than 1 mg. per minute (see dosage). Rapid administration can cause bradycardia, hypersalivation leading to respiratory difficulties and possibly convulsions.

An overdosage of ANTILIRIUM can cause a cholinergic crisis.

PRECAUTIONS: Because of the possibility of hypersensitivity in an occasional patient, atropine sulfate injection should always be at hand since it is an antagonist and antidote for physostigmine.

ADMINISTRATION AND DOSAGE: The usual adult dose of ANTILIRIUM is 0.5 to 2.0 mg. intramuscularly or intravenously. Intravenous administration should be at a slow, controlled rate of no more than 1 mg. per minute. It may be necessary to repeat dosages of 1 mg. to 4 mg. at intervals as life threatening signs such as arrhythmias, convulsions and deep coma recur.

IN ALL CASES OF POISONING, THE USUAL SUPPORTIVE MEASURES SHOULD BE UNDERTAKEN.

SUPPLIED: 2 ml. ampules containing:
PHYSOSTIGMINE SALICYLATE 1 mg. per ml.
Packed 12 ampules per box.

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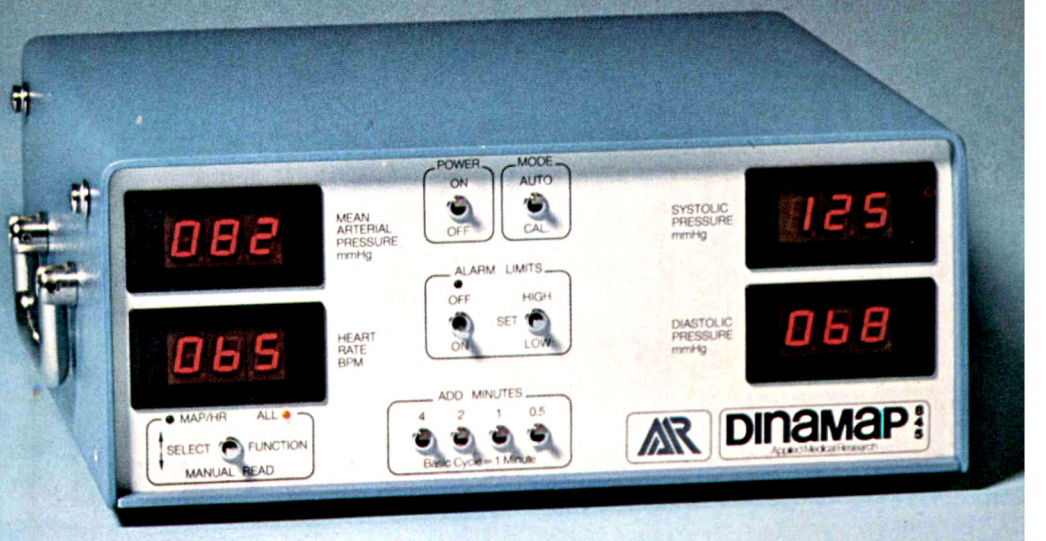
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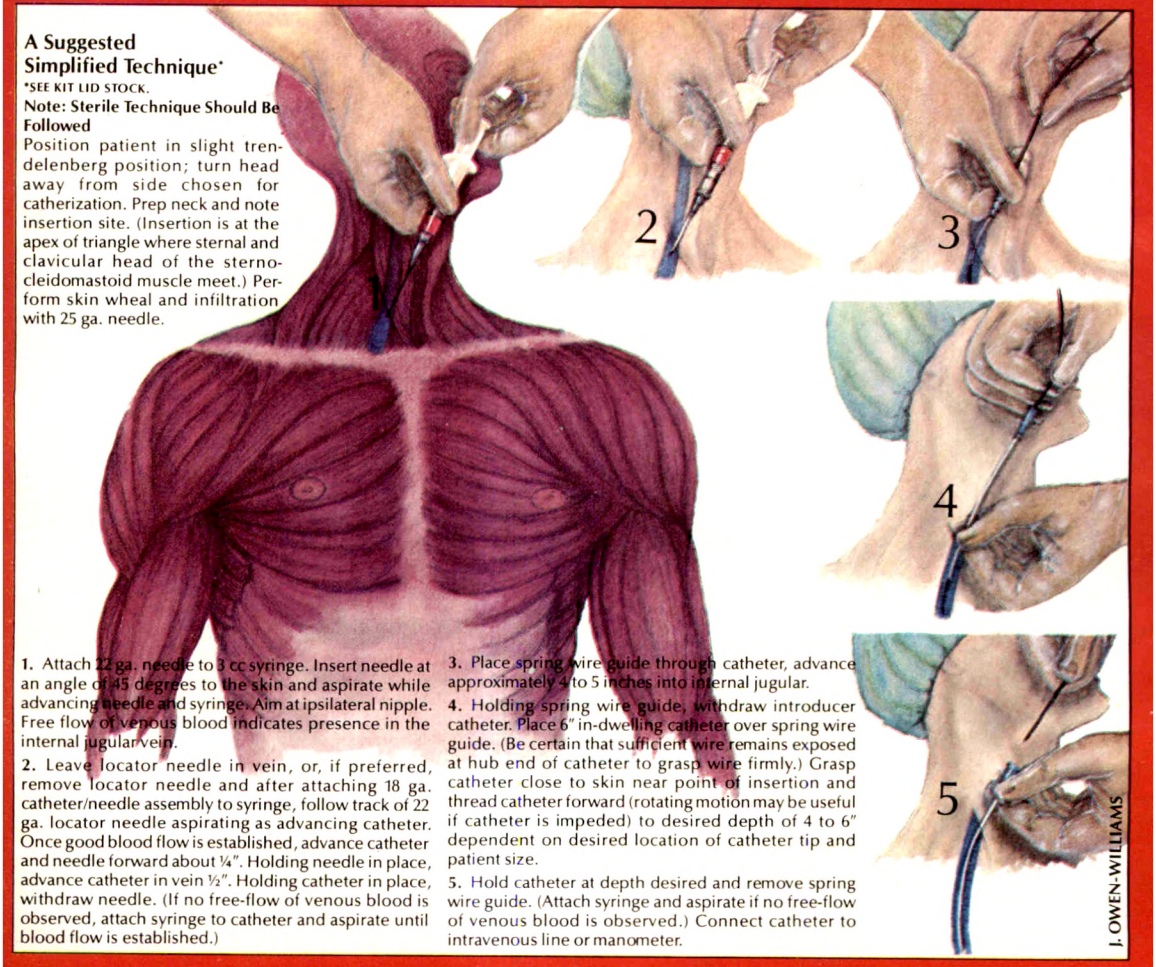
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2. Leave locator needle in vein, or, if preferred, remove locator needle and after attaching 18 ga. catheter/needle assembly to syringe, follow track of 22 ga. locator needle aspirating as advancing catheter. Once good blood flow is established, advance catheter and needle forward about ¼". Holding needle in place, advance catheter in vein ½". Holding catheter in place, withdraw needle. (If no free-flow of venous blood is observed, attach syringe to catheter and aspirate until blood flow is established.)

3. Place spring wire guide through catheter, advance approximately 4 to 5 inches into internal jugular.

4. Holding spring wire guide, withdraw introducer catheter. Place 6" in-dwelling catheter over spring wire guide. (Be certain that sufficient wire remains exposed at hub end of catheter to grasp wire firmly.) Grasp catheter close to skin near point of insertion and thread catheter forward (rotating motion may be useful if catheter is impeded) to desired depth of 4 to 6" dependent on desired location of catheter tip and patient size.

5. Hold catheter at depth desired and remove spring wire guide. (Attach syringe and aspirate if no free-flow of venous blood is observed.) Connect catheter to intravenous line or manometer.

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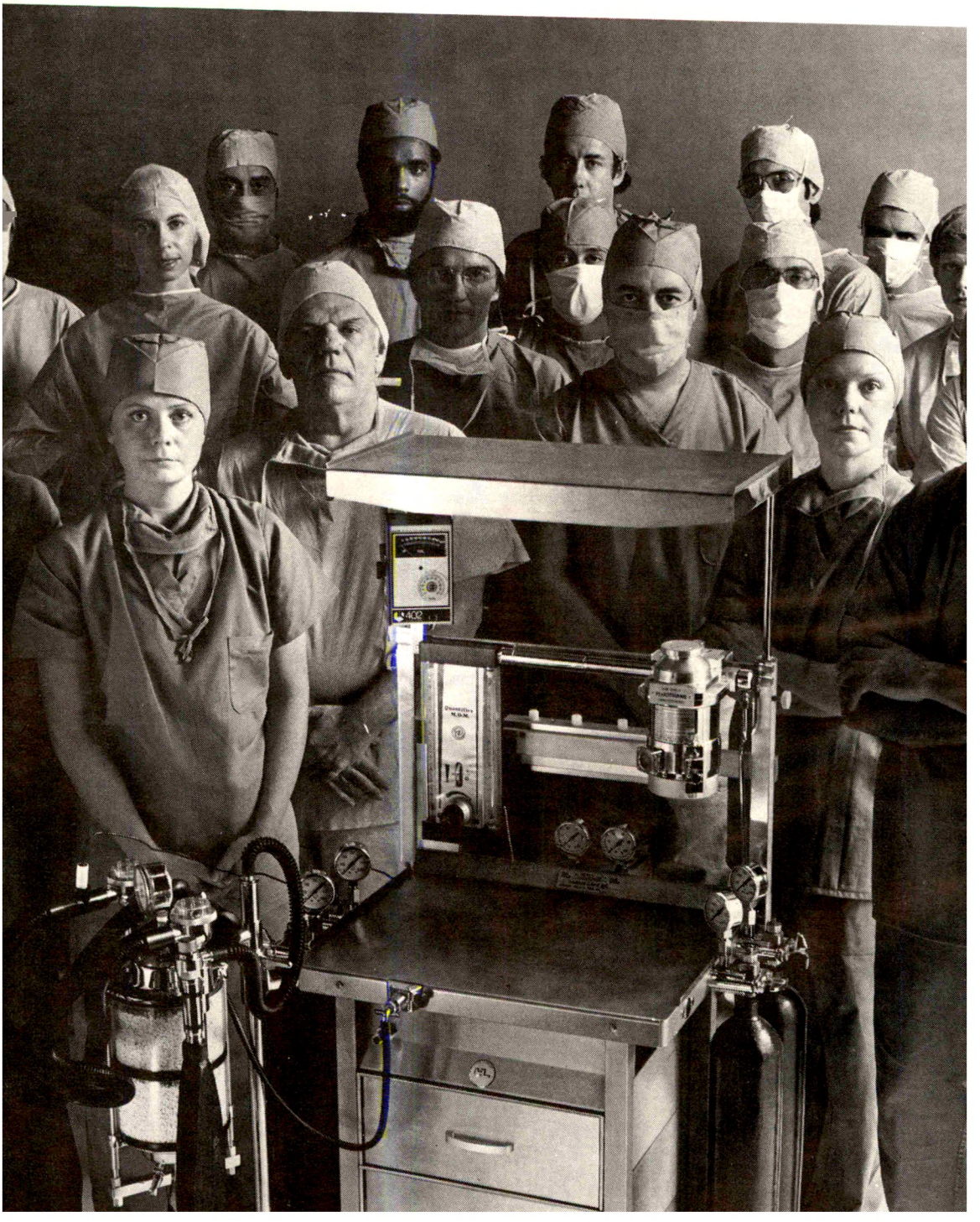
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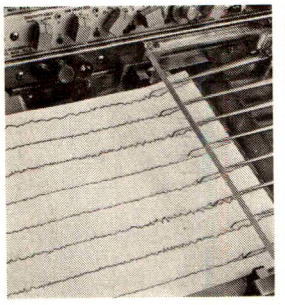
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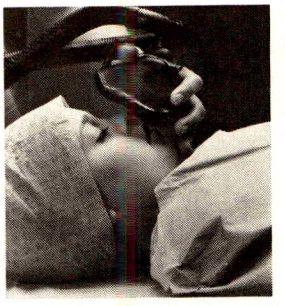
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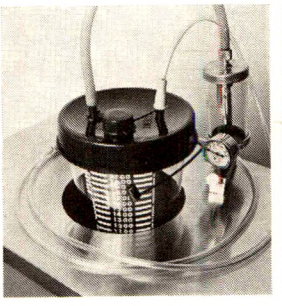
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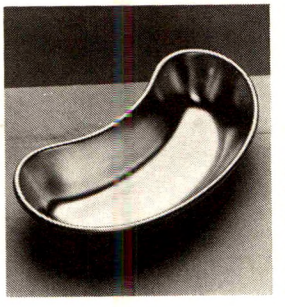




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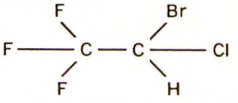
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FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane, U.S.P.) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all the diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE (halothane, U.S.P.) is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy. Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane, U.S.P.) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

Adverse Reactions. The following adverse reactions have been reported: hepatic necrosis, cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

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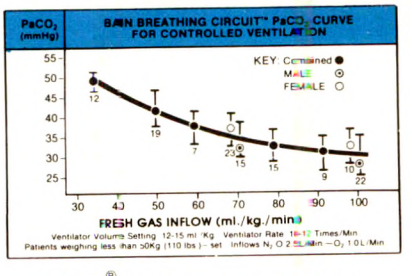
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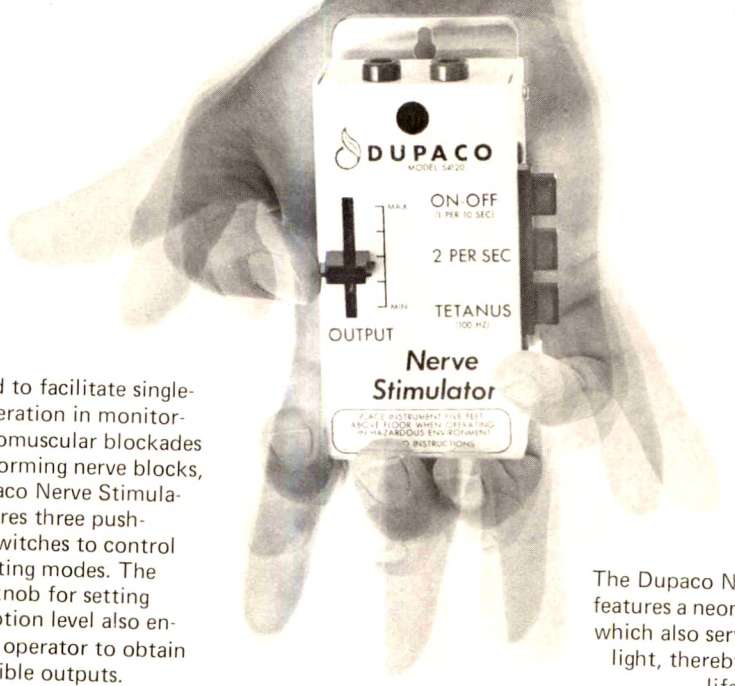
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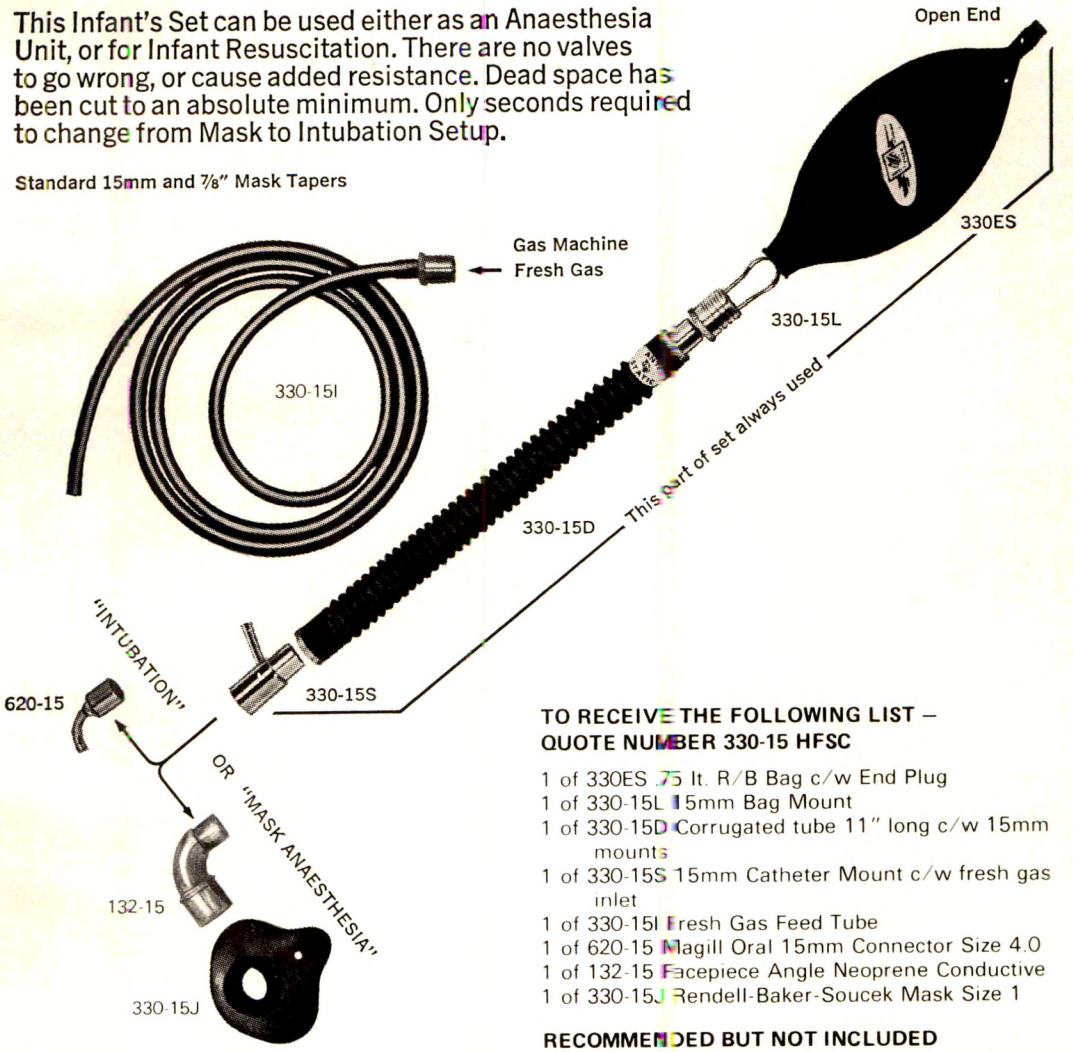
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1 of 330-15J Rendell-Baker-Soucek Mask Size 1

RECOMMENDED BUT NOT INCLUDED

6 (1 each) 674/330 Foregger Coles Tubes 8 to 18 F.G.
1 No. 330-15K Rendell-Baker-Soucek Mask Size 2
1 No. 330-15H Rendell-Baker-Soucek Mask Size 3
1 330LC Leather Case
1 of 330-15D Corrugated tube c/w 15mm mounts.

MIE

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A division of Claudius Ash Incorporated
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SEND FOR COMPLETE LITERATURE

in selected cases of shock

24mg/ml

INJECTION

DECADRON® PHOSPHATE

(DEXAMETHASONE SODIUM PHOSPHATE | MSD)

Contraindications: Systemic fungal infections (See **Warnings** re amphotericin B); hypersensitivity to any component.

Warnings: Corticosteroids may exacerbate systemic fungal infections and should not be used in presence of such infections unless needed to control reactions to amphotericin B; there have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive failure. In patients subjected to unusual stress, increase dosage of rapidly acting corticosteroids before, during, and after the stressful situation. Corticosteroids may mask some signs of infection; new infections, decreased resistance, and inability to localize infection may occur. Moreover, corticosteroids may affect the nitroblue-tetrazolium test for bacterial infection and produce false negative results. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and glaucoma with possible damage to optic nerves and may enhance the establishment of secondary, fungal or viral ocular infections.

Usage in pregnancy: In pregnancy or women of childbearing potential, weigh anticipated benefits against possible hazards to mother and embryo or fetus. Infants of mothers on substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism. Corticosteroids appear in breast milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other unwanted effects; mothers taking pharmacologic doses of corticosteroids should be advised not to nurse.

Elevation of blood pressure, salt and water retention, and increased excretion of potassium may occur with large doses of synthetic corticosteroids; dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion. Patients on corticosteroids should not be vaccinated against smallpox and other immunization procedures should not be undertaken except in those receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

In active tuberculosis, use should be restricted to fulminating or disseminated tuberculosis and should be in conjunction with appropriate antituberculous regimen; in latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur, and patients should receive chemoprophylaxis during prolonged corticosteroid therapy.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to parenteral administration, especially in patients with history of drug allergy.

Precautions: This steroid is sensitive to heat and should not be autoclaved. Drug-induced secondary adrenocortical insufficiency, which may be minimized by gradual reduction of dosage, may persist for months after discontinuation of therapy. In any situation of stress occurring during that period, hormone therapy should be reinstituted. If patient already is receiving steroids, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or mineralocorticoid should be administered concurrently.

In hypothyroidism and in cirrhosis, there is an enhanced effect of corticosteroids. Use cautiously in patients with ocular herpes simplex for fear of corneal perforation.

The lowest possible dose should be used, and when reduction in dosage is possible, it must be gradual. Psychic derangements may appear, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations, and existing emotional instability or psychotic tendencies may be aggravated. Psychological and/or physiological dependency may develop with long-term use; withdrawal symptoms include anorexia, vague pains, weakness, and lethargy. In hypoprothrombinemia, use aspirin cautiously in conjunction with corticosteroids.

Use with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection; also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Fat embolism has been reported as a possible complication of hypercortisonism. When large corticosteroid doses are given, some authorities advise that antacids be administered between meals to help to prevent peptic ulcer.

Growth and development of infants and children on prolonged therapy should be carefully followed. Motility and number of spermatozoa may be increased or decreased. Phenytoin, phenobarbital, ephedrine, and rifampin may enhance the metabolic clearance of corticosteroids, resulting in decreased blood levels and lessened physiologic activity, thus requiring adjustment in corticosteroid dosage; these interactions may interfere with dexamethasone suppression

drugs. Prothrombin time should be checked frequently in patients receiv concomitant coumarin anticoagulants because of reports that corticosterc have altered the response to these anticoagulants; studies have shown usual effect to be inhibition of response to coumarins, although there h been some reports of potentiation. When corticosteroids are administe concomitantly with potassium-depleting diuretics, patients should be served closely for development of hypokalemia.

Intra-articular injection may produce systemic as well as local effec Appropriate examination of any joint fluid present is necessary to exclud septic process. Marked increase in pain accompanied by local swelling, furt restriction of joint motion, fever, and malaise is suggestive of septic arthri if this complication occurs and diagnosis of sepsis is confirmed, appropri antimicrobial therapy should be instituted. Injection of a steroid into infected site is to be avoided. Corticosteroids should not be injected i unstable joints. Patients should be impressed strongly with the importanc not overusing joints in which symptomatic benefit has been obtained as l as the inflammatory process remains active. Frequent intra-articular inject may result in damage to joint tissues. The slower rate of absorption intramuscular administration should be recognized.

Adverse Reactions: *Fluid and electrolyte disturbances*—Sodium ret tion; fluid retention; congestive heart failure in susceptible patients; pot sium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal*—Mus weakness; steroid myopathy; loss of muscle mass; osteoporosis; verteb compression fractures; aseptic necrosis of femoral and humeral hea pathologic fracture of long bones. *Gastrointestinal*—Peptic ulcer w possible subsequent perforation and hemorrhage; pancreatitis; abdomi distention; ulcerative esophagitis. *Dermatologic*—Impaired wound heali thin fragile skin; petechiae and ecchymoses; erythema; increased sweati may suppress reactions to skin tests; burning or tingling, especially in t perineal area (after IV injection); other cutaneous reactions, such as aller dermatitis, urticaria, angioneurotic edema. *Neurologic*—Convulsions; creased intracranial pressure with papilledema (pseudotumor cerebri) usu after treatment; vertigo; headache. *Endocrine*—Menstrual irregularit development of cushingoid state; suppression of growth in children; seco ary adrenocortical and pituitary unresponsiveness, particularly in times stress, as in trauma, surgery, or illness; decreased carbohydrate toleran manifestations of latent diabetes mellitus; increased requirements for ins or oral hypoglycemic agents in diabetics. *Ophthalmic*—Posterior subcapsu cataracts; increased intraocular pressure; glaucoma; exophthalm *Metabolic*—Negative nitrogen balance due to protein catabolism. *Other* Anaphylactoid or hypersensitivity reactions; thromboembolism; weight ga increased appetite; nausea; malaise; psychological and/or physiologi dependency. *Additional* adverse reactions related to parenteral corticosteri therapy: Rare instances of blindness associated with intralesional thera around the face and head; hyperpigmentation or hypopigmentation; subcu neous and cutaneous atrophy; sterile abscess; postinjection flare (followi intra-articular use); Charcot-like arthropathy.

Note: Injection, 4 mg/ml — *For intravenous, intramuscular, intra-articul intralesional, and soft-tissue injection.* Injection, 24 mg/ml — *For intrav nous injection only. DOSAGE REQUIREMENTS ARE VARIABLE AND MU BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE AND THE RESPON OF THE PATIENT.*

How Supplied: Injection in two concentrations: Injection, 4 mg/ml, in 1- disposable syringes and 1-ml, 5-ml, and 25-ml vials, containing per r dexamethasone sodium phosphate equivalent to 4 mg dexamethasone pho phate or 3.33 mg dexamethasone; Inactive ingredients per ml: 8 r creatinine, 10 mg sodium citrate, sodium hydroxide to adjust pH, water injection q.s., with 1 mg sodium bisulfite, 1.5 mg methylparaben, and 0.2 r propylparaben added as preservatives; Injection, 24 mg/ml, in 5-ml and 10- vials, containing per ml: dexamethasone sodium phosphate equivalent 24 mg dexamethasone phosphate or 20 mg dexamethasone; Inactive ing dients per ml: 8 mg creatinine, 10 mg sodium citrate, 0.5 mg disodi edetate, sodium hydroxide to adjust pH, water for injection q.s., with 1 sodium bisulfite, 1.5 mg methylparaben, and 0.2 mg propylparaben added preservatives.

For more detailed information, consult your MSD representative or see full prescribing information.
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MSI
MERC
SHAR

in shock

unresponsive to conventional therapy
if adrenocortical insufficiency is suspected

24mg/ml

INJECTION

DECADRON® PHOSPHATE
(DEXAMETHASONE SODIUM PHOSPHATE | MSD)

high potency • low volume





240 mg – 10-ml vial
equivalent to 1000 mg
methylprednisolone

120 mg – 5-ml vial
equivalent to 500 mg
methylprednisolone

For IV use only. Easily identified as the high-potency concentration of Injection DECADRON® Phosphate – look for the red band on the carton and vial.

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continue your professional education. . . . . earn 26 credit hours annually



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Begins August 19

in shock

unresponsive to conventional therapy
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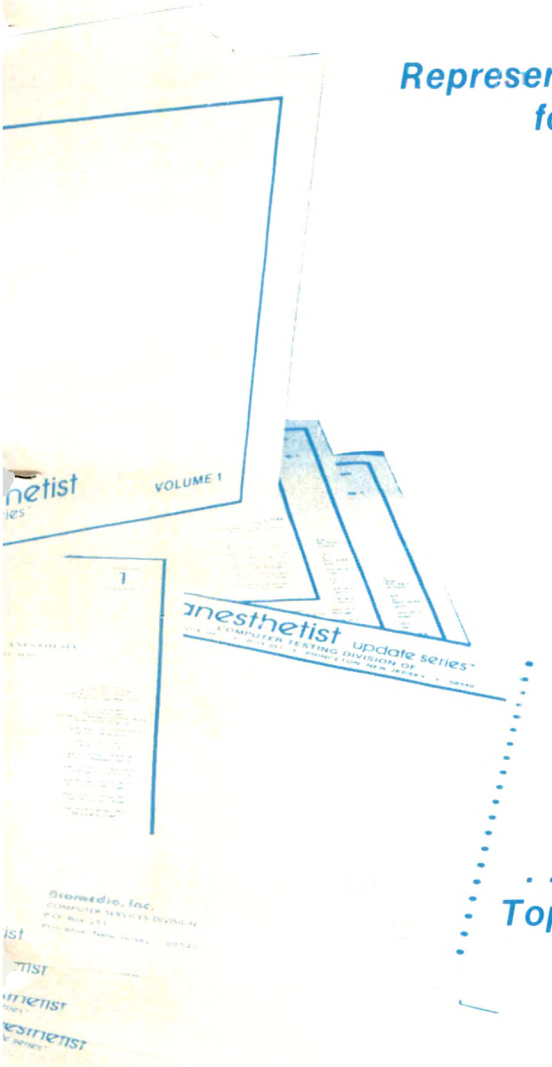
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Begins August 19



Representative Topics for this Series

- Acid-Base Balance
- Fluids and Electrolytes
- Blood Gas Analysis and Treatment
- Conduction Anesthesia—Pharmacology
- Deliberate Hypotensive Anesthesia
- Pre-Operative Assessment
- EKG—Interpretation and Treatment
- Geriatric Anesthesia
- Respiratory Mechanisms and Considerations
- Vasopressors
- Legal Aspects and Implications
- Anesthesia for Neurosurgery
- Pediatric Anesthesia
- Nerve Block for Extremities
- O.B. Anesthesia
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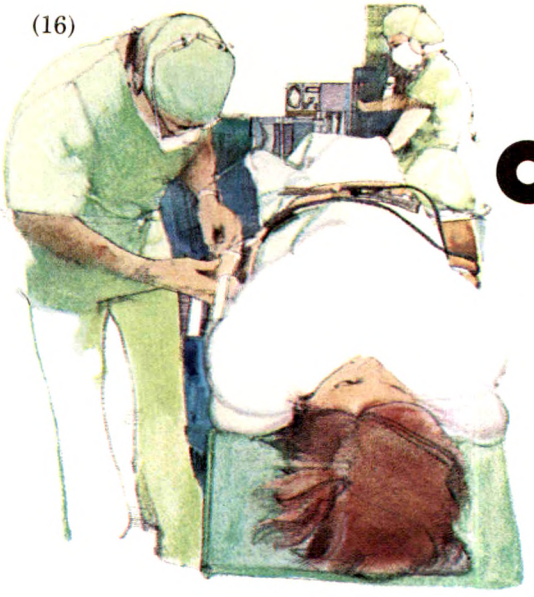
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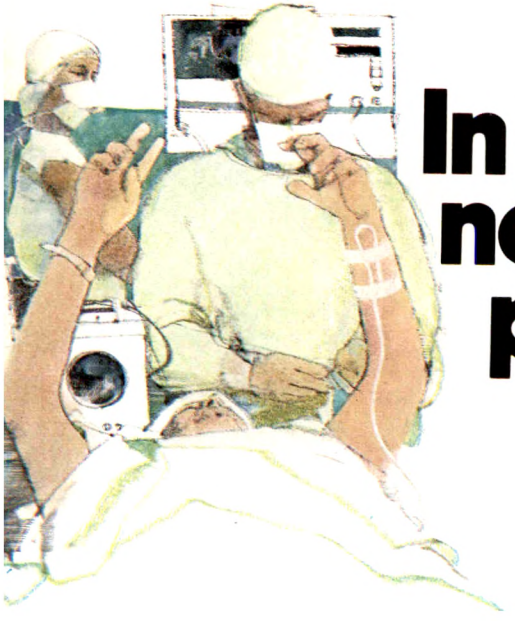
In general or regional anesthesia

when you need a flexible narcotic supplement

In outpatient procedures

when you want rapid emergence with minimal "hangover" effect





In diagnostic or neurosurgical procedures

when you want the patient to change position or respond to commands

Potent narcotic analgesic action... with an added dimension of control

SUBLIMAZE® (fentanyl) provides:

- Profound analgesia with minimal cortical depression
- Rapid onset of analgesia – peak effect within 5 minutes I.V., 8 minutes I.M.
- Short duration of analgesic action – 30 to 60 minutes with a single I.V. dose of up to 0.1 mg. (Respiratory depressant effects may last longer than the analgesia.)
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SUBLIMAZE® C II
(fentanyl) injection

0.05 mg./ml. as the citrate Sodium hydroxide for adjustment of pH to 4.0–7.5

Warning: May be habit forming

SUBLIMAZE® (fentanyl) injection is available for use only upon direction of a physician.

For information relating to Contraindications, Warnings, Precautions, and Adverse Reactions for SUBLIMAZE fentanyl, please turn pa

Potent narcotic analgesic action.. with an added dimension of contr

SUBLIMAZE® (C II)

(fentanyl) injection

0.05 mg./ml. as the citrate Sodium hydroxide for adjustment of pH to 4.0–7.5

Warning: May be habit forming

INDICATIONS SUBLIMAZE (fentanyl) is indicated:

– for analgesic action of short duration during the anesthetic periods, premedication, induction, and maintenance, and in the immediate postoperative period (recovery room) as the need arises.

– for use as a narcotic analgesic supplement in general or regional anesthesia.

– for administration with a neuroleptic such as *INAPSINE*® (droperidol) injection as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia.

CONTRAINDICATIONS SUBLIMAZE (fentanyl) is contraindicated in patients with known intolerance to the drug.

WARNINGS AS WITH OTHER CNS DEPRESSANTS, PATIENTS WHO HAVE RECEIVED SUBLIMAZE (fentanyl) SHOULD HAVE APPROPRIATE SURVEILLANCE.

RESUSCITATIVE EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

See also discussion of narcotic antagonists in Precautions and Overdosage.

If SUBLIMAZE (fentanyl) is administered with a tranquilizer such as *INAPSINE* (droperidol), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used *fluids and other countermeasures to manage hypotension should be available.*

As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE (fentanyl) persists longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as 1/4 to 1/3 those usually recommended. SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. The effect is related to the speed of injection and its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

Drug Dependence – SUBLIMAZE (fentanyl) can produce drug dependence of the morphine type and therefore has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE (fentanyl) in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure – SUBLIMAZE (fentanyl) should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition, SUBLIMAZE (fentanyl) may obscure the clinical course of patients with head injury.

Usage in Children – The safety of SUBLIMAZE (fentanyl) in children younger than two years of age has not been established.

Usage in Pregnancy – The safe use of SUBLIMAZE (fentanyl) has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

PRECAUTIONS *The initial dose of SUBLIMAZE (fentanyl) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses.*

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms (see Actions) SUBLIMAZE (fentanyl) can also alter respiration. Therefore, when SUBLIMAZE (fentanyl) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia. When used with a tranquilizer such as *INAPSINE* (droperidol), blood pressure may be altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE (fentanyl) should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory res and others with potentially compromised respiration. In such patients, narc may additionally decrease respiratory drive and increase airway resist During anesthesia, this can be managed by assisted or controlled respir Respiratory depression caused by narcotic analgesics can be reverse narcotic antagonists. Appropriate surveillance should be maintained bec the duration of respiratory depression of doses of fentanyl employed d anesthesia may be longer than the duration of the narcotic antagonist ac Consult individual prescribing information (levallorphan, nalorphine naloxone) before employing narcotic antagonists.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIM (fentanyl), pulmonary arterial pressure may be decreased. This fact shoul considered by those who conduct diagnostic and surgical procedures w interpretation of pulmonary arterial pressure measurements might deter final management of the patient.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, general anesthetics) will have additive or potentiating effects with SUBLIM (fentanyl). When patients have received such drugs, the dose of SUBLIM (fentanyl) required will be less than usual. Likewise, following the admini tion of SUBLIMAZE (fentanyl), the dose of other CNS depressant drugs sh be reduced.

SUBLIMAZE (fentanyl) should be administered with caution to patients with and kidney dysfunction because of the importance of these organs ir metabolism and excretion of drugs.

SUBLIMAZE (fentanyl) may produce bradycardia, which may be treated atropine; however, SUBLIMAZE (fentanyl) should be used with caution ir tients with cardiac bradyarrhythmias.

When SUBLIMAZE (fentanyl) is used with a tranquilizer such as *INAP* (droperidol), hypotension can occur. If this occurs, the possibili hypovolemia should also be considered and managed with appropriate pa teral fluid therapy. Repositioning the patient to improve venous return to heart should be considered when operative conditions permit. Care shoul exercised in moving and positioning of patients because of the possibili orthostatic hypotension. If volume expansion with fluids plus other counterr sures do not correct hypotension, the administration of pressor agents c than epinephrine should be considered. Because of the alpha-adrene blocking action of *INAPSINE* (droperidol), epinephrine may paradoxically crease the blood pressure in patients treated with *INAPSINE* (droperidol When *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) and the EE used for postoperative monitoring, it may be found that the EEG pattern ret to normal slowly.

ADVERSE REACTIONS As with other narcotic analgesics, the most com serious adverse reactions reported to occur with SUBLIMAZE (fentanyl) respiratory depression, apnea, muscular rigidity, and bradycardia; if th remain untreated, respiratory arrest, circulatory depression or cardiac ar could occur.

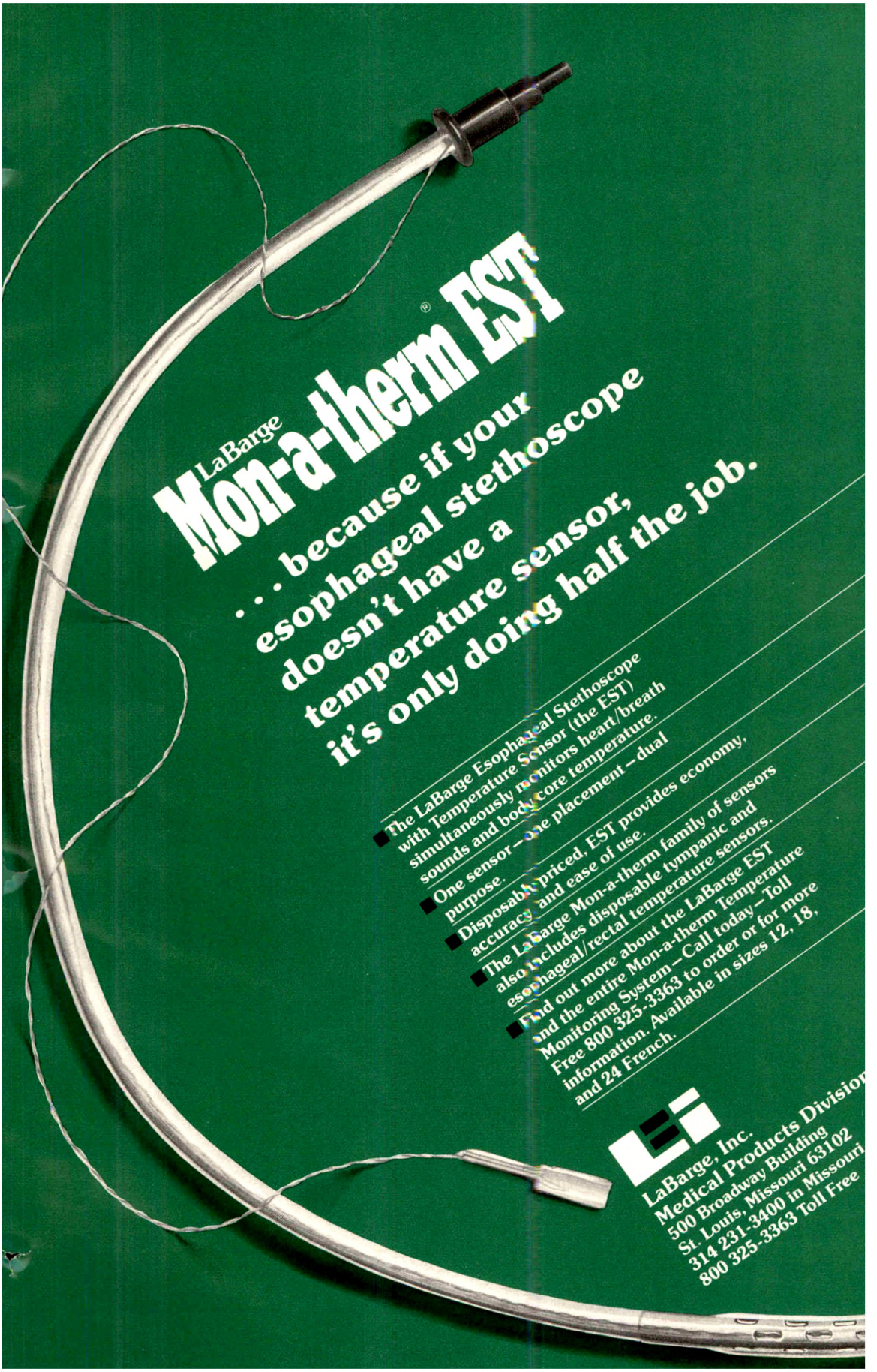
Other adverse reactions that have been reported are hypotension, dizzin blurred vision, nausea, emesis, laryngospasm, and diaphoresis.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIM (fentanyl), the following adverse reactions can occur: chills and/or shiver restlessness, and postoperative hallucinatory episodes (sometimes associ with transient periods of mental depression); extrapyramidal symptoms (tonia, akathisia, and oculogyric crisis) have been observed up to 24 h postoperatively. When they occur, extrapyramidal symptoms can usuall controlled with anti-Parkinson agents. Postoperative drowsiness is also quently reported following the use of *INAPSINE* (droperidol).

Elevated blood pressure, with and without pre-existing hypertension, has b reported following administration of SUBLIMAZE (fentanyl) combined wit *APSINE* (droperidol). This might be due to unexplained alterations in syn thetic activity following large doses; however, it is also frequently attribute anesthetic and surgical stimulation during light anesthesia.

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NARCAN®
naloxone HCl
NEUTRALIZES THE NEGATIVE

NARCAN® reverses narcotic-induced respiratory depression

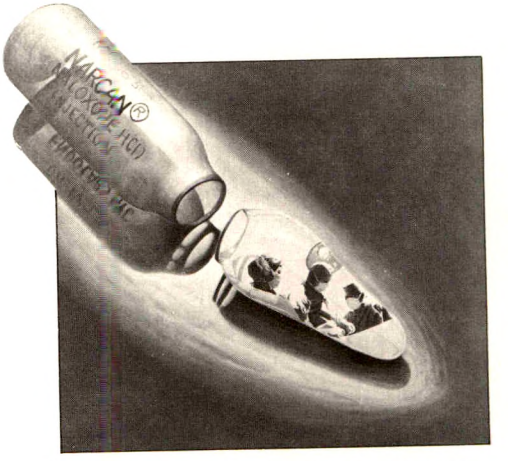
has no morphine-like activity

- will not cause any depression of its own or augment non-narcotic depression
- dosage can be titrated to reverse respiratory depression and maintain adequate analgesia

Useful when narcotic/N_2O anesthesia is employed

Potent, reliable and fast acting

- response is usually evident within 2-3 minutes after I.V. administration and only slightly longer I.M.
- can be used I.V., I.M. or subcutaneously according to the patient's need for immediacy and duration of narcotic antagonism



The duration of activity of some narcotics may exceed that of NARCAN.® Observe the patient closely and give repeat doses of NARCAN® if needed.

Also available, NARCAN® NEONATAL naloxone HCl

Please see next page for complete prescribing information.

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Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
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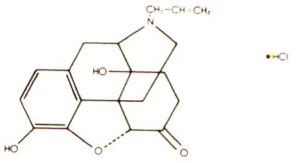
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NARCAN® is an Endo registered U.S. trademark; U.S. Pat. 3,254,088

NARCOTIC SUPPLEMENTED ANESTHESIA

NARCAN®
naloxone HCl

DESCRIPTION NARCAN® (naloxone hydrochloride), a narcotic antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.



NALOXONE HYDROCHLORIDE
(-)-17-Allyl-4, 5α-epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride

Naloxone hydrochloride occurs as slightly off-white crystals, and is soluble in water, slightly soluble in alcohol and practically insoluble in ether.

NARCAN® (naloxone hydrochloride) Injection is available in two concentrations, 0.02 mg and 0.4 mg of naloxone hydrochloride per ml. Each ml of either strength contains 8.6 mg of sodium chloride; and 2.0 mg of methylparaben and propylparaben as preservatives in a ratio of 9 to 1. pH is adjusted with hydrochloric acid.

ACTIONS NARCAN® (naloxone hydrochloride) is an essentially pure narcotic antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other narcotic antagonists; NARCAN® (naloxone hydrochloride) does not produce respiratory depression, psychotomimetic effects or pupillary constriction. In the absence of narcotics or agonistic effects of other narcotic antagonists it exhibits essentially no pharmacologic activity.

In the presence of physical dependence on narcotics NARCAN® (naloxone hydrochloride) will produce withdrawal symptoms; it has not been shown to produce tolerance nor to cause physical or psychological dependence.

When NARCAN® (naloxone hydrochloride) is administered intravenously the onset of action is generally apparent within two minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration of NARCAN® (naloxone hydrochloride). Intramuscular administration produces a more prolonged effect than intravenous administration. The requirement for repeat doses of NARCAN® (naloxone hydrochloride), however, will also be dependent upon the amount, type and route of administration of the narcotic being antagonized.

INDICATIONS NARCAN® (naloxone hydrochloride) is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by natural and synthetic narcotics, propoxyphene and the narcotic-antagonist analgesic pentazocine. NARCAN® (naloxone hydrochloride) is also indicated for the diagnosis of suspected acute opiate overdosage.

CONTRAINDICATIONS NARCAN® (naloxone hydrochloride) is contraindicated in patients known to be hypersensitive to it.

WARNINGS NARCAN® (naloxone hydrochloride) should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

The patient who has satisfactorily responded to NARCAN® (naloxone hydrochloride) should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride).

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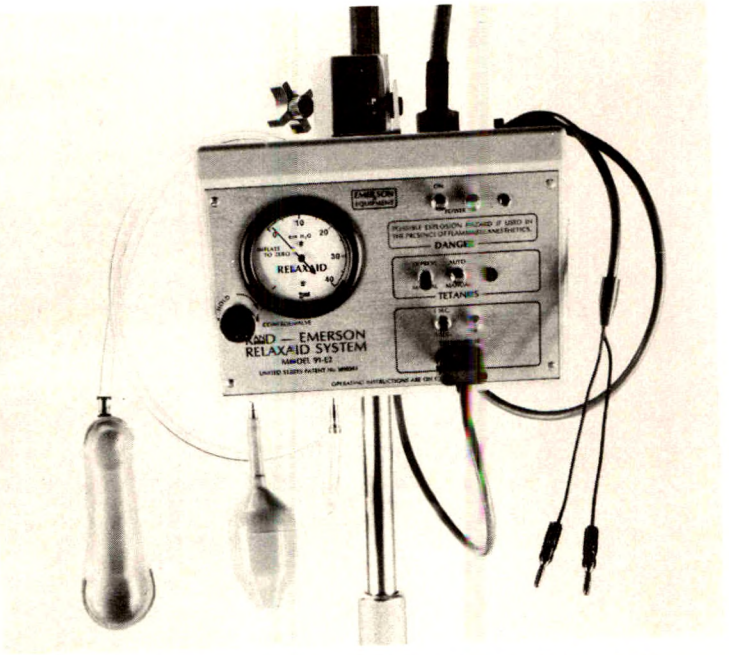
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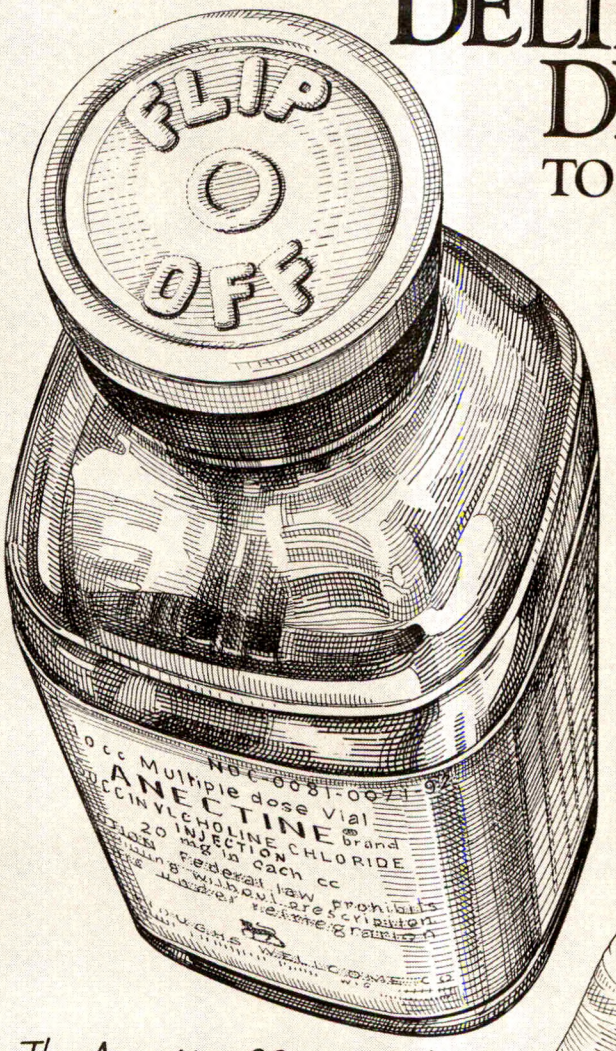
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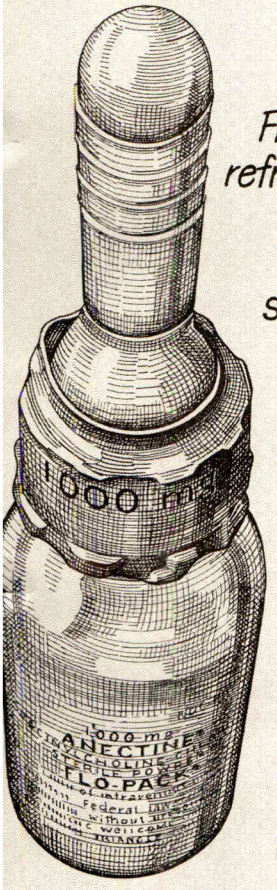
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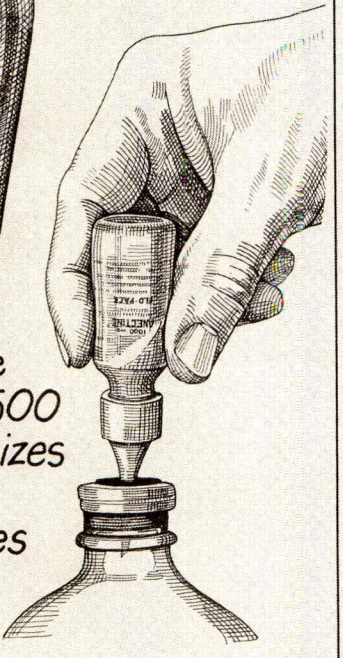
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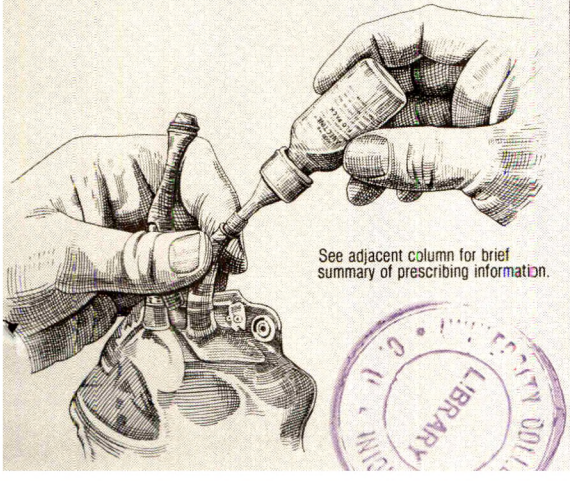
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Succinylcholine should not be mixed with short-acting barbiturates in the same syringe or administered simultaneously through the same needle. Solutions of succinylcholine have an acid pH whereas those of barbiturates are alkaline in reaction. Depending upon the resultant pH of a mixture of the solutions of these drugs, either free barbituric acid may be precipitated or succinylcholine hydrolyzed.

Usage in pregnancy: Safe use of succinylcholine has not been established with respect to possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential, particularly during early pregnancy, unless in the physician's judgment, the potential benefits outweigh the unknown hazards.

PRECAUTIONS: Low levels or abnormal variants of plasma cholinesterase may be associated with prolonged respiratory depression or apnea following use of succinylcholine. Low levels of plasma cholinesterase may occur in patients with severe liver disease or cirrhosis, severe anemia, malnutrition, severe dehydration, changes in body temperature, exposure to neurotoxic insecticides or those receiving antimalarial drugs. Succinylcholine should be administered at minimal dosage and with extreme care to such patients. If low plasma cholinesterase is suspected, a small test dose of from 5 to 10 mg of succinylcholine may be administered or relaxation may be produced by cautious administration of a 0.1% solution of the drug by intravenous drip. Drugs which either inhibit plasma cholinesterase such as neostigmine or phospholine iodide, or compete with succinylcholine for the enzyme, as does intravenous procaine, should not be given concurrently.

Succinylcholine should be administered with great caution to patients with severe burns, those recovering from severe trauma, those suffering from electrolyte imbalance, those receiving quinidine, those who have been digitalized recently or who may have digitalis toxicity as serious cardiac arrhythmias or cardiac arrest may result. Patients with pre-existing hyperkalemia or who are paraplegic, have suffered spinal neuraxis injury or have degenerative or dystrophic neuromuscular disease tend to become severely hyperkalemic when succinylcholine is given. Succinylcholine given over a long period of time may change the characteristic depolarization block of the myoneural junction to a nondepolarizing block resulting in prolonged respiratory depression or apnea. In such cases, small repeated doses of neostigmine may possibly act as an antagonist. A peripheral nerve stimulator may be used to determine the type of neuromuscular blockade. If a depolarization block is present, both fast (tetanic) and slow (twitch) rates of nerve stimulation are well-sustained and post-tetanic facilitation is absent. If a nondepolarizing block is present, there is a post-tetanic facilitation and "fade" of successive stimuli on both fast (tetanic) and slow (twitch) rates of nerve stimulation. Succinylcholine should be used with caution during ocular surgery and in patients with glaucoma. Patients with fractures or muscle spasm may suffer additional trauma if fasciculations are induced. Muscle fasciculations and hyperkalemia may be reduced by administering a small dose of a nondepolarizing relaxant. If other relaxants are to be used during the same period, the possibility of a synergistic or antagonistic effect should be considered. In recent years a fulminant syndrome, malignant hyperthermia, has been reported and observed during anesthesia. Its etiology is not fully understood. It occurs in genetically prone individuals of all ages and both sexes receiving potent anesthetics such as halothane, methoxyfluothane, cyclopropane and diethyl ether. It appears to develop irrespective of concomitant use of a muscle relaxant but may be triggered by succinylcholine. Because of the seriousness of malignant hyperthermia and the need for early, effective treatment, continuous monitoring of the patient temperature is suggested.

ADVERSE REACTIONS: Profound and prolonged muscle relaxation may occur, resulting in respiratory depression to the point of apnea. Hypersensitivity to the drug may exist in rare instances. The following adverse reactions have been reported: bradycardia, tachycardia, hypertension, hypotension, arrhythmias, cardiac arrest, prolonged respiratory depression or apnea, hyperthermia, increased intraocular pressure, muscle fasciculation, postoperative muscle pain, myoglobinemia and excessive salivation.

MANAGEMENT OF ADVERSE REACTIONS: Apnea or prolonged muscle paralysis should be treated with controlled respiration. The use of neostigmine to reverse nondepolarization block is a medical decision which must be made on the basis of individual clinical pharmacology and the experience and judgment of the clinician. When neostigmine is used, atropine should also be administered.

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Editorial

Systemic Toxicity of Local Anesthetic Agents

As the use of regional anesthetic techniques in clinical medicine increases, the potential systemic toxicity of local anesthetic drugs takes on added importance. The systemic toxicity of local anesthetic agents essentially involves the central nervous system and the cardiovascular system. The central nervous system is particularly prone to the toxic actions of local anesthetic drugs. Symptoms such as dizziness, ringing in the ears, vague sensations of lightheadedness, nystagmus and fine skeletal muscle twitching in face and digits are usually observed as the initial indications of local anesthetic toxicity. As the blood level and, presumably, brain level of the local anesthetic agent rises, overt convulsions of a tonic and clonic nature may occur, followed by CNS depression when seizure activity terminates and respiratory efforts become shallow and, ultimately, cease. Adverse reactions to local anesthetic agents are usually believed due to a rapid inadvertent intravenous injection, administration into a highly vascular anatomical site, or the extravascular administration of an excessive amount of drug.

It is not difficult to explain the adverse effects which occur following the rapid inadvertent intravenous injection of a full anesthetic dose. For example, 20 ml of 1.5% lidocaine (300 mg) without epinephrine is commonly employed for lumbar epidural anesthesia. The peak blood level following the epidural injection of lidocaine 300 mg would be approximately 3 μg/ml, which is rarely associated with adverse effects. However, if this 300 mg dose of lidocaine is inadvertently administered rapidly into a peripheral vein, the resultant high blood level would tend to cause symptoms of CNS toxicity. Similarly, the extravascular administration of an excessive amount of drug should be associated with signs of systemic toxicity. A peak blood level of approximately 1 μg/ml is achieved for every 100 mg of lidocaine administered into the lumbar epidural space. Since blood levels in excess of 5 μg/ml of lidocaine are usually required to produce signs of systemic toxicity, one may anticipate some toxicity if doses greater than 500 mg of lidocaine are injected epidurally at one time.

Toxic responses to relatively small doses of local anesthetic agents, eg, less than 50 mg of lidocaine, are rare, but occasionally do occur. The etiology of these reactions is unclear, particularly when one is aware that 50 to 100 mg of an agent such as lidocaine are routinely administered intravenously to cardiac patients for the control of ventricular arrhythmias. Various investigators have attributed such reactions to allergy, idiosyncrasy, or decreased tolerance without any sound scientific rationale for these explanations.

The paper by Aldrete and coworkers in this issue offers a possible mechanism for the CNS toxicity associated with the injection of relatively small amounts of a local anesthetic agent. These authors have demonstrated in this and previous publications that the intra-arterial injection of local anesthetic agents under pressure can produce a retrograde flow which will permit a high concentration of local anesthetic drug to reach the cerebral circulation.[1] In such a situation, a relatively small dose of the local anesthetic agent administered intra-arterially may result in a level of drug in the brain sufficient to cause a toxic reaction. As shown in the present study by Aldrete and coworkers the injection of lidocaine 3 mg/kg into the lingual artery can result in a concentration of approximately 30 μg/ml in the internal carotid artery. This lidocaine arterial level markedly exceeds the venous blood levels which are associated with signs of toxicity in human subjects.[2] Moreover, this concentration also exceeds the mean

arterial lidocaine level of 18 μg/ml which was reported by Munson et al as the convulsive threshold level in monkeys.[3]

The other important and interesting observation is that the intra-arterial injection of lidocaine in a vessel at some distance from the head can also lead to extremely high anesthetic levels in the internal carotid artery. For example, injections into the brachial artery of lidocaine 7 mg/kg resulted in a peak lidocaine level in excess of 100 μg/ml in the internal carotid artery 6 seconds after injection. This, again, may explain some of the toxic reactions reported to local anesthetics following brachial plexus blockade by the axillary approach. In this particular technic it is not uncommon to actually penetrate the axillary artery. It may be possible in these situations for a portion of the injected anesthetic dose to be delivered into the axillary artery under pressure, which would then find its way retrograde into the cerebral circulation and so produce signs of CNS toxicity even in the presence of an effective brachial plexus block.

One aspect of the study by Aldrete and coworkers does require further clarification. The blood level values reported in figs 2, 3, 4, and 6 consistently show higher venous plasma levels than arterial plasma levels at 15 to 180 seconds following injection into an arterial vessel. This suggests that tissue binding sites for lidocaine may have been exceeded, such that free drug exists in the intra or extracellular space which diffuses back into capillary beds as the intra-arterial concentration of lidocaine falls below the extravascular concentration. Studies in the literature in which arterial and venous samples have been taken concomitantly have shown that the venous level is consistently lower than the arterial level for approximately 30 to 60 minutes following injection of the local anesthetic agent.[4] However, it is fair to say that in these studies the drug was administered either intravenously or into a peripheral tissue site, such as the epidural space, so that the arterial concentration was rather low. Nonetheless, it would appear that further studies are warranted to determine the reason for the consistently higher venous levels reported in the present study.

It should be apparent from the present study by Aldrete and coworkers and other reports in the literature that a reassessment of the factors responsible for the potential systemic toxicity of local anesthetic agents is necessary. In particular, it is clear that we can no longer state the maximum safe dose of a local anesthetic agent without defining the conditions under which the agent is administered. For example, it has been clearly shown that the rate of absorption from various extravascular anatomical injection sites is markedly different. The use of the same dose of a local anesthetic agent for intercostal nerve blockade will result in significantly higher blood levels than an injection into the epidural space.[5] What is a "safe" dose for each regional anesthetic technic? The most common cause of adverse reactions to local anesthetics is an inadvertent intravascular injection. Usually this involves administration into a peripheral vein. What are the factors that influence the toxicity of local anesthetic agents administered by the intravenous route? Finally, we should consider the possible toxicity of inadvertent intra-arterial injections. This may become increasingly important as the use of small gauge needles, such as the 27-gauge needles employed in dentistry, increases. What is the relative toxicity of different local anesthetic agents when administered into various arterial vessels? The answer to most of these questions, of necessity, must come from animal experiments. However, the relationship of toxicity studies conducted in animals to the clinical situation involving man also requires careful reevaluation.[6]

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Renal Blood Flow: Differences in Autoregulation During Anesthesia with Halothane, Methoxyflurane, or Alphaprodine in the Dog

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The hypothesis that general anesthesia impairs the ability of the kidney to regulate its blood flow was examined in 15 dogs during anesthesia with halothane, halothane and N_2O, methoxyflurane, alphaprodine, or alphaprodine and N_2O. Anesthesia was induced with halothane in 5 experiments and with thiopental in all the remainder. Blood pressure was altered by dextran infusion and by controlled hemorrhage, and changes in renal blood flow were monitored by using chronically implanted Doppler ultrasonic flow probes. Our results show that autoregulation of renal blood flow was maintained during halothane anesthesia, despite a significant decrease in arterial pressure ($p = 0.0005$); only when the normal lower autoregulatory limit of pressure was reached did renal blood flow decrease. During anesthesia with methoxyflurane or alphaprodine, renal blood flows were reduced during controlled hemorrhage before the normal lower autoregulatory limit of pressure was reached. Autoregulation was, therefore, impaired by these agents. Induction of anesthesia with thiopental did not alter the response of renal blood flow to dextran or hemorrhage during halothane administration. Nitrous oxide did not significantly alter renal blood flow responses during halothane, alphaprodine, or methoxyflurane anesthesia.

Key Words—KIDNEY, blood flow. ANESTHETICS, volatile, halothane. ANESTHETICS, volatile, methoxyflurane. ANESTHETICS, intravenous, alphaprodine.

ALTHOUGH it has been stated that anesthesia alters the ability of the kidney to autoregulate its blood flow,[1] it has been shown that halothane does not disturb autoregulation in the isolated dog kidney.[2] However, in the intact animal, the response of renal blood flow to alterations in systemic pressure during anesthesia may differ from that which is observed in the isolated organ. Furthermore, anesthetics may differ in their effects on autoregulation of renal blood flow. The present experiments were designed to study the effects of several different anesthetics on autoregulation of blood flow in the intact dog kidney.

METHODS

Preparation

Fifteen male mongrel dogs (average weight 20.25 kg, range 16 to 28 kg) were anesthetized with thiopental and halo-

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thane,* and the left renal arteries were exposed extraperitoneally through a flank incision. Doppler† ultrasonic flow probes, previously calibrated with polyethylene tubing, whole blood, and a variable-volume pump were placed around the arteries as previously described.[3] Leads from the probes were passed subcutaneously and exteriorized at the back of the neck. The animals were allowed to recover for at least 4 days. During this time they were fed standard Purina chow and allowed unlimited tap water.

The dogs were trained to lie quietly on their right sides before the surgical preparation and they became accustomed to sphygmomanometric estimation of blood pressure using a pediatric (6.5-cm) cuff and auscultation of the brachial artery. The procedure was repeated frequently throughout the training period. Mean pressure was determined by employing the formula: MAP = diastolic pressure + 1/3 pulse pressure.

Before experiments were carried out, the animals were fasted for 17 hours but allowed free access to water.

Experimental Protocol

Blood pressure and renal blood flow were recorded in awake tranquil animals at the beginning of each experiment. Anesthesia then was induced as described below and maintained by inhalation agents alone or in combination with alphaprodine. The animals were placed upon their right sides. After endotracheal intubation, they were ventilated by a Bird Mark 8 ventilator. One femoral artery was cannulated percutaneously and blood pressure was measured by a Statham transducer (P23AC), the output from which was displayed on a Grass model-7 polygraph. Blood gases were measured using a Radiometer PHM71 and, by adjusting ventilation, were maintained at $Pao_2 > 100$ torr, $Paco_2$ 30 to 40 torr, and pH 7.36 to 7.45. Rectal temperatures were measured and maintained at 38 C by means of a warming blanket. End-tidal halothane concentrations were measured by a Beckman LB2 infrared analyzer. Five percent dextrose and H_2O were infused at 100 ml/hr through a forelimb vein.

Once steady arterial-pressure and blood-gas readings were obtained, 400 ml dextran 75 in 6% saline were infused rapidly. Five percent dextrose was discontinued during dextran infusion, which took approximately 20 minutes.

The effect upon renal blood flow of whatever increase in arterial pressure followed the infusion of dextran was observed. Blood pressure was permitted to stabilize at its new level for 10 to 15 minutes, 2000 units of heparin were administered IV, and blood was then withdrawn via the arterial line in 200-ml increments until mean arterial pressure was 40 to 50 mm Hg. Hypotension was maintained for approximately 10 minutes. This proved sufficient time for renal blood flow to stabilize and to permit arterial sampling and gas analysis. Blood which had been withdrawn was then warmed to body temperature and returned to the animal.

All dogs were allowed a recovery period of at least 4 days before another experiment was carried out.

Anesthetic Subgroups

Group 1: Halothane (Five Dogs)—(a) Five experiments: Induction and maintenance in this subgroup were with halothane and O_2. Maintenance end-tidal halothane was 1.25% to 1.4%.

(b) Five experiments: Anesthesia was induced with thiopental (20 mg/kg) and maintained with halothane and O_2 (1.25% to 1.4% end-tidal).

(c) Five experiments: Anesthesia was induced with thiopental (20 mg/kg) and maintained with halothane (1 to 1.2% end-tidal) and N_2O (inspired concentration, 70%).

Group 2: Methoxyflurane — Five dogs (different dogs from those used in the halothane subgroup) and 5 experiments: Anesthesia was induced with thiopental (20 mg/kg) and maintained with methoxyflurane (1% in O_2) via a Pentec vaporizer.

Group 3: Alphaprodine—Seven dogs (2 of whom had previously been exposed to methoxyflurane once) in 10 experiments: Anesthetic induction was with thiopental (20 mg/kg). The animals were then subjected to endotracheal intubation and positive pressure ventilation, after which an IV infusion of 0.05 mg/ml alphaprodine in 5% dextrose was started, preceded by a bolus of 12 mg alphaprodine at the commencement of the infusion. The rate of infusion was adjusted so that there was no response of blood pressure or pulse rate to the stimulus of a tail-squeeze with an artery forcep, and this infusion rate was maintained

*Kindly supplied by Hoechst Pharmaceuticals Ltd.
†Parks Electronics Inc., Beaverton, Oregon

throughout the experiment. Pancuronium 0.06 mg/kg was given IV when the alphaprodine infusion was commenced. Additional increments of 0.01 to 0.02 mg/kg were administered as required to prevent limb movement.

Two sets of experiments were performed. In both subgroups the induction of anesthesia was with thiopental (20 mg/kg).

(a) Five dogs in 5 experiments: Maintenance of anesthesia was with alphaprodine and O_2.

(b) Five dogs in 5 experiments (2 dogs previously exposed to methoxyflurane): Anesthetic maintenance was with alphaprodine and N_2O (70% inspired concentration).

Student's *t*-test was employed for statistical analysis.

RESULTS

Halothane (Figure 1)—Half an hour after anesthesia was started, in those animals where N_2O was not employed, arterial blood pressure was lower than the awake level (average reduction, 23.3%; $p<0.001$). In the presence of N_2O, there was no significant change in blood pressure. In all animals anesthetized with halothane, the induction of anesthesia was followed by a nonsignificant decrease in renal blood flow.

Dextran infusion produced an average increase in arterial pressure of 20% above the postinduction level ($p<0.02$). There was no change in renal blood flow following dextran infusion.

When blood pressure was reduced by controlled hemorrhage, renal blood flow did not change until a mean pressure of 70 mm Hg was reached, at which point it started to decrease. When blood was reinfused, renal blood flow increased until the same mean arterial pressure (70 mm Hg) was achieved. No further increase in flow rate occurred thereafter, despite the continued rise in pressure. Neither the induction of anesthesia with thiopental nor the concomitant administration of N_2O altered the response of renal blood flow to changes in arterial pressure following dextran infusion or controlled hemorrhage.

Methoxyflurane (Figure 2)—After induction of anesthesia with thiopental and maintenance with methoxyflurane, arterial pressure decreased 13.9% (p = n.s.) and renal blood flow decreased 11% ($p<0.025$). When blood pressure rose following dextran infusion, renal blood flow showed a similar change; and as controlled hemorrhage lowered pressure, there was also an accompanying fall in renal blood flow.

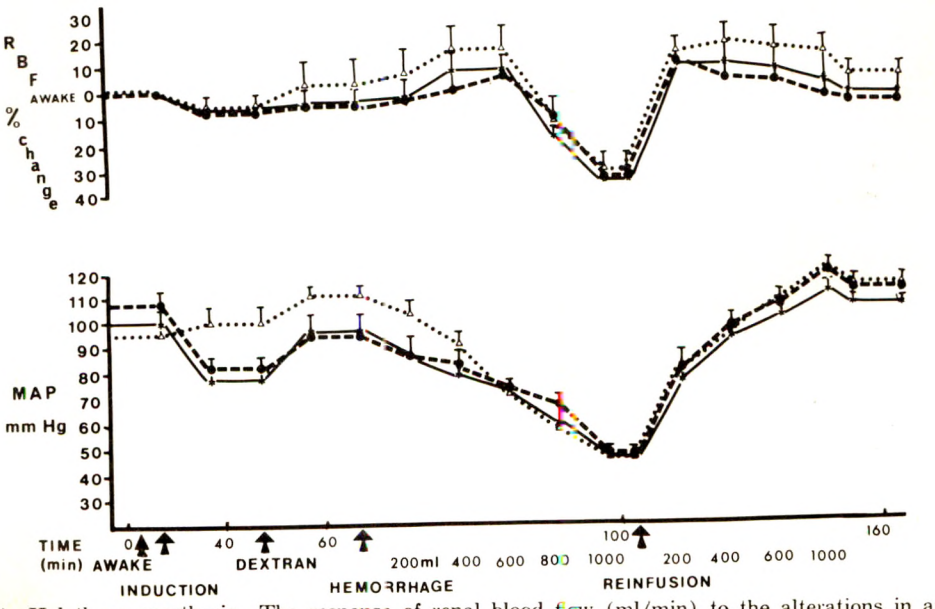


FIG 1. Halothane anesthesia. The response of renal blood flow (ml/min) to the alterations in arterial blood pressure which follow the infusion of dextran or controlled hemorrhage.

• • △ • • = thiopental, halothane, and N_2O-O_2
— — ● — — = halothane-O_2
—— * —— = thiopental and halothane-O_2

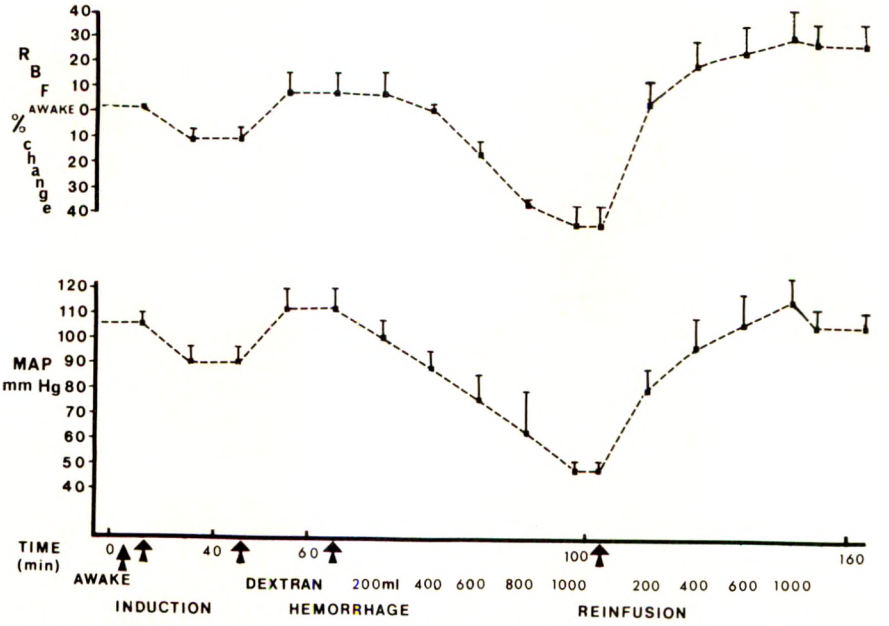


FIG 2. Methoxyflurane-O_2 anesthesia. The response of renal blood flow (ml/min) to changes in arterial blood pressure following infusion of dextran or controlled hemorrhage.

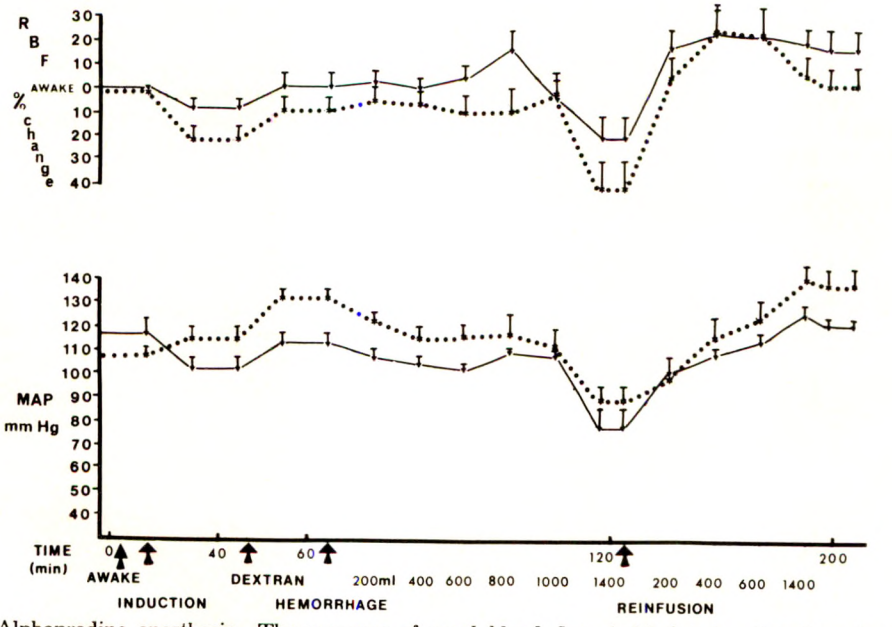


FIG 3. Alphaprodine anesthesia. The response of renal blood flow (ml/min) to alterations in arterial blood pressure following infusion of dextran or controlled hemorrhage.
—— —— = alphaprodine-O_2
• • * • • = alphaprodine and N_2O-O_2

Alphaprodine (Figure 3)—After the induction of anesthesia (alphaprodine and thiopental), blood pressure fell 12.5% (n.s.) when N_2O was not used and rose 6.5% (n.s.) in those animals where N_2O was administered.

The induction of anesthesia was accompanied by a decrease in renal blood flow. Without N_2O, this was 8.1% ($p<0.05$); and with N_2O, the reduction was 21.4% ($p<0.01$).

Dextran infusion caused a nonsignificant increase in blood pressure ($p<0.1$) in animals anesthetized with alphaprodine alone,

and a significant increase ($p<0.05$) when N_2O was combined with alphaprodine In neither case was the infusion of dextran accompanied by a significant change in renal blood flow.

When controlled blood loss was produced during alphaprodine anesthesia, arterial pressure did not decrease until considerably more blood was removed than was the case during anesthesia with halothane or methoxyflurane. In animals anesthetized with alphaprodine (with or without N_2O), it was necessary to remove up to 45.9 ml/kg before a reduction in blood pressure below the postinduction level was produced, whereas 21.5 ml/kg was sufficient to initiate a reduction in pressure during halothane or methoxyflurane anesthesia.

However, during anesthesia with alphaprodine, any decrease in mean arterial pressure was accompanied by a reduction in renal blood flow.

DISCUSSION

In 1905 Pringle et al observed that anesthesia with diethyl ether was accompanied by a decreased output of urine, which they attributed to inhibition of "renal activity" by the anesthetic.[4] Since publication of this observation, numerous investigators have studied the effects of anesthesia upon renal function.[5-7] It has become apparent, however, that the effect of general anesthesia on renal function is complex. For example, although it has been stated that "all general anesthetics significantly diminish renal plasma flow, glomerular filtration rate and water and electrolyte excretion, if there is sufficient depth of anesthesia,"[8] since most general anesthetics depress cardiovascular activity and diminish arterial blood pressure when administered in sufficient concentrations and since renal plasma flow and glomerular filtration are functions of renal blood flow (itself intimately related to arterial pressure), this statement does little more than suggest the possibility that the renal effects of anesthetics may be related to anesthetically induced alterations in arterial pressure.

In normal conscious dogs renal blood flow is not affected by changes in arterial pressure. The kidney, in fact, autoregulates its own perfusion to such an extent that, between 200 mm Hg and 70 mm Hg mean systemic pressure, renal perfusion remains relatively constant.[9,10]

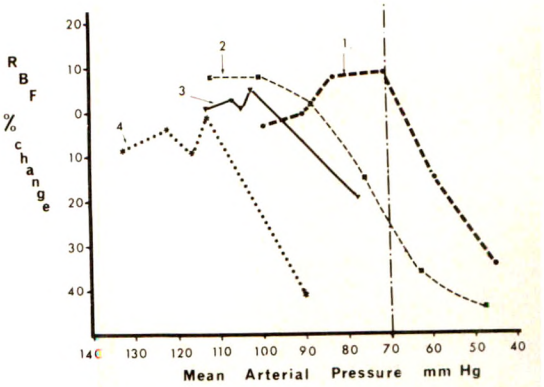


FIG 4. The response of renal blood flow (ml/min) to reduction in arterial pressure (left to right on horizontal axis) during anesthesia with halothane, methoxyflurane, and alphaprodine. Note normal lower limit of autoregulation at 70 mm Hg.

1 = halothane
2 = methoxyflurane
3 = alphaprodine
4 = alphaprodine and N_2O

It has been stated that "autoregulation of renal blood flow is of interest because it appears to be abolished during general anesthesia."[1] If this is true, then a decrease in mean arterial pressure during anesthesia should be associated with parallel reduction in renal blood flow and, similarly, an increase in pressure should increase renal perfusion.

On the other hand, should autoregulation persist in the kidney during general anesthesia with some or all anesthetic agents, then renal perfusion will decrease only when mean arterial pressure is reduced below the lower limit of autoregulation. Such a reduction in pressure might provide one explanation for the reduced urine output observed by Pringle et al and others although, obviously, other possible explanations exist, including increased circulating levels of antidiuretic hormone, catecholamine release, and activation of the renin-angiotensin system.

Figure 4, which summarizes the results of the present experiments, shows that renal autoregulation is maintained during halothane anesthesia; renal blood flow does not start to decrease until mean arterial pressure falls below 70 mm Hg, the same point at which autoregulation fails in unanesthetized animals.[11]

The experiments which we report here show that halothane does not alter the capacity of the dog kidney to autoregulate its blood flow in response to changes in ar-

terial pressure produced by rapid increase in blood volume or by hemorrhage. The preservation of autoregulation is unaffected by N_2O or induction of anesthesia with thiopental.

On the other hand, methoxyflurane anesthesia, as has been reported elsewhere (and confirmed in the present series of experiments), impairs the autoregulation of renal blood flow.[3]

During anesthesia with alphaprodine and pancuronium, autoregulation of renal blood flow also was not maintained. The addition of N_2O to alphaprodine anesthesia in the dog produced a decrease in renal blood flow in response to hemorrhage which was greater than that which occurred in the presence of alphaprodine without N_2O.

De Wardener and Miles have shown that the pressure-flow curve of renal blood flow during hemorrhage suggests that sustained vasoconstriction abolishes the ability of the kidney to alter its perfusion.[12] It is possible that this explains the response of the kidney during alphaprodine anesthesia. The addition of N_2O may enhance the constriction of the renal vessels. This degree of renal vasoconstriction may perhaps be a function of light narcotic-muscle relaxant technics of anesthesia. If this is so, then the clinical implications are obvious, and even comparatively minor blood loss may lead to an appreciable decrease in renal perfusion.

The present experiments demonstrate that autoregulation of renal blood flow is maintained during halothane anesthesia, but is lost during anesthesia with methoxyflurane or alphaprodine.

ACKNOWLEDGMENT

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Acetate Fails to Reverse Myocardial Depression in Dogs Anesthetized with Halothane

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Sodium acetate has been shown to reverse the myocardial depression induced by halothane in vitro. The biochemical basis for this restoration of contractility has been located in the glycolytic pathway. The present study was designed to determine whether this antagonistic property of acetate also occurs in vivo. Dogs autonomically blocked with guanethidine, phenoxybenzamine, and atropine were sequentially anesthetized with halothane in O_2 and N_2O-O_2-succinylcholine in a random pattern. All animals were given sodium acetate IV in amounts adequate to produce pharmacologically active levels. Myocardial performance was measured by $LVdP/dt_{max}$, $LVdP/dt/KP_{max}$, and V_{max}. Halothane effected a significant depression of these myocardial parameters. Acetate did not reverse this depressant effect of halothane. Acetate, a well-established peripheral vascular vasodilator, did decrease left ventricular and aortic pressures.

Key Words—ANESTHETICS, volatile, halothane. HEART, myocardial function.

ACETATE, pyruvate, lactate, and fructose, when administered in vitro, reverse the halothane-induced depression of myocardial contractility.[1-4] This antagonistic effect is apparently secondary to a bypassing of blockade produced by halothane of the glucose phosphate isomerase-mediated step in the glycolytic pathway. The present study investigated whether sodium acetate would also reverse the depression of myocardial contractility induced by halothane in vivo, and thus serve as a clinically useful drug.

METHODS

Six unpremedicated mongrel dogs weighing 16.4 ± 0.1 kg were anesthetized with halothane and endotracheally intubated. In 3 dogs, anesthesia was then maintained for the first half of the study period with 1.4 ± 0.1% halothane (inspired) in O_2, and during the second half with 70% N_2O and 30% O_2 plus IV succinylcholine (1 mg/min). The sequence in which anesthetics were administered in the other 3 dogs was reversed.

Autonomic blockade was produced in each dog. In order to achieve sympathetic blockade, 4 dogs received 15 mg/kg IV guanethidine 18 hours prior to anesthesia, plus an additional 5 mg/kg IV immediately after induction of anesthesia; 2 dogs received 15 mg/kg guanethidine IV 30 minutes prior to induction.[5,6] In addition, 3 of the dogs received 5 mg/kg phenoxybenzamine IV prior to the N_2O half of the experiment. Each dog also received 3.5 mg/kg atropine IV immediately prior to the beginning of each half of the experiment to maintain a

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blockade of the parasympathetic system and the sympathetic cholinergic vasodilator fibers.[6,7]

Ventilation was controlled to maintain $Paco_2$ and pH in the normal range, mean values being $Paco_2$ = 35 ± 2 torr, and pH = 7.37 ± 0.02. The Pao_2 was 166 ± 6 torr when the Fio_2 = 0.3 and 592 ± 26 torr when the Fio_2 = 1.0. Body temperature was maintained at 38.6 ± 0.6 C by external heating lamps and blankets.

A 19-gauge, 100-cm aortic arch catheter* for recording aortic pressure (AP) was placed percutaneously via one femoral artery and an 18-gauge, short catheter† was placed in the other femoral artery for blood sampling. A 4-inch, 18-gauge catheter‡ for recording left ventricular pressure (LVP) was placed percutaneously through the left chest wall. Pressures were recorded by Statham P23 Gb strain gauges. The frequency response of the entire system was flat to 100 Hz. Electrocardiogram and average heart rate (HR) were also obtained. This information was recorded on both a multichannel polygraph and magnetic tape. The LVP was processed through an analog computer to provide values for $LVdP/dt_{max}$ and $LVdP/dt/KP_{max}$, where P = developed pressure, and K = 24.7.[8] Our three-amplifier differentiator had a linear response to 150 Hz at the settings used in this study. The LVP was filtered before computation, thus eliminating both the necessity for filtering the derivative and the subsequent phase shift between LVP and LV dP/dt. This phase shift can create gross inaccuracies in the calculation of LV dP/dt/KP. The LV dP/dt/KP was displayed as a continuous function of P on a storage oscilloscope, and values for the maximal intrinsic velocity of contraction (V_{max}) were obtained by extrapolating P to zero value.

After a steady state of anesthesia was established, sterile solutions of similar molarity of sodium acetate (NaAc, 15 g/100 ml), sodium chloride (NaCl, 12 g/100 ml), or sodium bicarbonate ($NaHCO_3$, 15 g/100 ml) were infused IV for 10 minutes. The NaCl and $NaHCO_3$ infusion served as, respectively, osmolarity and buffer base controls for the NaAc infusions. The NaAc was infused at a rate of 0.1, 0.3, or 1.0 ml/min (0.18, 0.55, and 1.83 mEq/min) and the control infusions of NaCl or $NaHCO_3$ at a rate of 1.0 ml/min (2.05 and 1.79 mEq/min). The sequence of infusions for each dog was determined by random selection. Recordings were obtained during the 4-minute preinfusion control period, during the 10-minute infusion, and again during the 4-minute period following the infusion. For analytic purposes, the 10-minute treatment period was divided into 3 segments: first 4 minutes (early), next 3 minutes (middle), and last 3 minutes (late). Arterial blood was sampled during each of the first 4 study periods and analyzed for $Paco_2$, pH, serum sodium, potassium, osmolarity, and acetate. Blood glucose concentrations were stable throughout the experiments (97 ± 7 mg/100 ml).

Serum acetate concentrations of 3 dogs were measured by a modification of the acetate kinase assay,[9] which involved addition of a known amount of acetate kinase activity* to a concentrated incubation medium. The resulting mixture consisted of 0.025 ml 2M Tris-HCl buffer (pH 7.4), 0.005 ml 2M $MgCl_2$, 0.085 ml 56% $NH_2OH.HCl$, 0.085 ml 8M KOH, 0.050 ml 0.2M ATP, and 0.070 ml acetate kinase; and 0.25 ml of the test or standard serum, with or without known amount of added sodium acetate, was incubated with this mixture for 10 minutes at 29 C. The reaction was stopped by the addition of 1 ml 10% trichloracetic acid and centrifuged at 10,000 rpm for 15 minutes. The supernate was added to 2 ml $FeCl_3$ in 2N HCl, centrifuged at 10,000 rpm for 5 minutes, and read in a colorimeter using the 540-mu filter. This assay was reproducibly accurate for quantification of serum acetate in the range of 10^{-4}M - 10^{-2}M.

Significance of differences between mean values of the two anesthetic groups and between successive experimental periods were tested by Student's *t*-test for paired data, and differences were considered significant when $p<0.05$.

RESULTS

Blood Chemistries — Serum sodium, potassium and osmolarity and blood buffer base were the same in the N_2O and halothane groups. Buffer base increased pro-

*Central Arterial Pressure Infusor, Sorenson Research Corp., 2511 South West Temple, Salt Lake City, Utah 84115

†Medicut® Cannula, Sherwood Medical Industries, St. Louis, Missouri 63103

‡Longdwell® Thin-Wall Catheter Needle (Teflon), Becton-Dickenson and Co., Rutherford, New Jersey 07070

*Sigma, St. Louis, Missouri

gressively throughout infusions of NaAc and $NaHCO_3$. The only change in serum potassium was a small decrease (0.2 mEq/L) that occurred during the late period of infusion of 1.0 ml/min NaAc. Serum sodium and osmolarity did not change.

Serum Acetate (Table 1)—Pooled data from 3 dogs demonstrated an increase in serum acetate levels during the 10 minutes of infusion, the largest change occurring with the highest infusion rate. The average molarity of the preinfusion sera was 1.4×10^{-4}M and the highest concentrations (average value 2.5×10^{-3}M) were achieved at the termination of the 1.0 ml/min infusion.

LVP, AP, HR (Tables 2, 3, 4)—When compared with values recorded during N_2O anesthesia, peak systolic LVP, mean AP, and average HR all significantly decreased during the administration of halothane. During halothane anesthesia, LVP, AP, and HR significantly decreased during the early part of the infusion of 1.0 ml/min NaAc. The LVP and HR returned to control values during the midinfusion period, and AP returned toward control values during the late infusion period. Following the NaAc infusion, LVP and AP rebounded to values greater than those of the late infusion period. Similar trends were noted in the N_2O group. Heart rate was significantly elevated in the early infusion period of $NaHCO_3$ during N_2O anesthesia.

Myocardial Performance (Table 5)—When compared with the values obtained during N_2O anesthesia, halothane anesthesia resulted in a significant decrease of $LVdP/dt_{max}$, $LVdP/dt/KP_{max}$, and V_{max}. The mean control values for V_{max} were 2.41 ± 0.07 sec^{-1} for N_2O anesthesia and 1.49 ± 0.03 sec^{-1} for halothane anesthesia. Small but significant increases in V_{max} were recorded in the early period of infusion of 0.1 ml/min NaAc and the middle period of infusion of $NaHCO_3$ during N_2O anesthesia, and in the middle period of infusion of 0.1 ml/min NaAc during halothane anesthesia. There were no significant alterations of $dP/dt/KP_{max}$.

TABLE 1
Serum Acetate (Molarity)*

Infusion	Rate	Preinfusion	Infusion		
			Early	Middle	Late
Sodium acetate	0.1 ml/min	$1.8 \pm 0.2 \times 10^{-4}$	$1.6 \pm 0.2 \times 10^{-4}$	$1.7 \pm 0.3 \times 10^{-4}$	$3.4 \pm 0.6 \times 10^{-4}$
Sodium acetate	0.3 ml/min	$1.0 \pm 0.2 \times 10^{-4}$	$3.0 \pm 0.4 \times 10^{-4}$	$5.2 \pm 0.8 \times 10^{-4}$	$5.3 \pm 0.8 \times 10^{-4}$
Sodium acetate	1.0 ml/min	$1.2 \pm 0.2 \times 10^{-4}$	$9.0 \pm 1.6 \times 10^{-4}$	$1.4 \pm 0.4 \times 10^{-3}$	$2.5 \pm 0.5 \times 10^{-3}$

*$\bar{x}$ ± SE; values obtained from 3 dogs, each receiving each infusion rate during both N_2O and halothane anesthesias.

DISCUSSION

Paradise and Ko demonstrated that acetate, lactate, pyruvate, and fructose reversed the depressant effect of halothane on myocardial contractility in both rat and human atrial strip preparations, a depressant effect associated with and ascribed to metabolic block at the glucose phosphate isomerase-

TABLE 2
Peak Left Ventricular Systolic Pressure (Torr)*

		n†	Preinfusion	Infusion			Postinfusion
				Early‡	Middle	Late	
N_2O							
Sodium acetate	0.1 ml/min	6	132 ± 14	133 ± 14(2.4)	132 ± 12	133 ± 13	130 ± 13
Sodium acetate	0.3 ml/min	6	130 ± 14	127 ± 12(4.3)	129 ± 12	131 ± 14	131 ± 13
Sodium acetate	1.0 ml/min	6	134 ± 11	128 ± 9(10.9)	135 ± 11	136 ± 11	137 ± 10
Sodium chloride	1.0 ml/min	5	137 ± 14	139 ± 13(2.3)	142 ± 12	144 ± 14	145 ± 13
Sodium bicarbonate	1.0 ml/min	3	118 ± 9	120 ± 9(1.7)	124 ± 8	129 ± 10	128 ± 12
Halothane							
Sodium acetate	0.1 ml/min	6	80 ± 5	79 ± 5(2.5)	80 ± 5	80 ± 5	80 ± 5
Sodium acetate	0.3 ml/min	6	77 ± 5	75 ± 5(8.2)	73 ± 4	76 ± 5	78 ± 5
Sodium acetate	1.0 ml/min	6	91 ± 5	79 ± 4§(23.6)	91 ± 5§	96 ± 5	102 ± 6
Sodium chloride	1.0 ml/min	4	82 ± 9	80 ± 9(4.8)	77 ± 8	75 ± 8	74 ± 8
Sodium bicarbonate	1.0 ml/min	3	96 ± 6	95 ± 5(5.5)	96 ± 6	99 ± 6	100 ± 5

*x ± SE
†n = number of dogs
‡Mean maximum initial depression (percent of control value) is displayed in parentheses.
§Difference of mean values of this and preceding period is significant ($p<0.05$).

TABLE 3
Mean Aortic Pressure (Torr)*

		n†	Preinfusion	Infusion			Postinfusion
				Early‡	Middle	Late	
N_2O							
Sodium acetate	0.1 ml/min	6	97 ± 16	96 ± 14(6.1)	98 ± 14	98 ± 15	97 ± 15§
Sodium acetate	0.3 ml/min	6	99 ± 13	94 ± 13(9.0)	96 ± 12	98 ± 12	99 ± 13
Sodium acetate	1.0 ml/min	6	97 ± 12	89 ± 13§(16.2)	97 ± 12	100 ± 12	104 ± 12
Sodium chloride	1.0 ml/min	5	105 ± 12	105 ± 11(4.1)	105 ± 11	109 ± 11	112 ± 12
Sodium bicarbonate	1.0 ml/min	3	79 ± 32	79 ± 22(1.8)	85 ± 19	89 ± 21	87 ± 23
Halothane							
Sodium acetate	0.1 ml/min	6	69 ± 5	69 ± 4(5.3)	69 ± 5	69 ± 5	70 ± 4
Sodium acetate	0.3 ml/min	6	68 ± 4	63 ± 3(18.3)	62 ± 5	65 ± 4	68 ± 4
Sodium acetate	1.0 ml/min	6	78 ± 4	59 ± 4§(38.1)	70 ± 3	78 ± 4	87 ± 4§
Sodium chloride	1.0 ml/min	4	73 ± 11	71 ± 11(7.7)	68 ± 10	65 ± 9	65 ± 10
Sodium bicarbonate	1.0 ml/min	3	83 ± 3	84 ± 4(3.2)	83 ± 3	84 ± 4	90 ± 3

See table 2 for meaning of symbols.

medicated step of the glycolytic pathway.[1-4] Similar findings have been reported for methoxyflurane.[10,11] Such reports contrast with the increase in glycolytic activity found in mouse heteroploid tissue cultures in which growth was inhibited by halothane.[12,13] The uptake of acetate is increased in rat hepatoma cells treated with halothane,[14] but the administration of acetate, pyruvate, and lactate failed to prevent halothane-induced inhibition of cell multiplication.[15] Thus it may be that the findings of Paradise and Ko are specific for their myocardial preparations. The important ques-

TABLE 4
Heart Rate (Beats/Min)*

				Infusion			
		n†	Preinfusion	Early‡	Middle	Late	Postinfusion
N_2O							
Sodium acetate	0.1 ml/min	6	178 ± 10	178 ± 10 (1.0)	176 ± 10	177 ± 10	178 ± 10
Sodium acetate	0.3 ml/min	6	175 ± 13	177 ± 13 (0.2)	177 ± 11	176 ± 11	175 ± 13
Sodium acetate	1.0 ml/min	6	175 ± 7	172 ± 7 (6.2)	176 ± 7	176 ± 6	177 ± 7
Sodium chloride	1.0 ml/min	5	192 ± 11	194 ± 11 (0.3)	193 ± 10	191 ± 11	188 ± 10
Sodium bicarbonate	1.0 ml/min	3	156 ± 0	160 ± 0§ (+2.5)	162 ± 2	168 ± 11	171 ± 15
Halothane							
Sodium acetate	0.1 ml/min	6	131 ± 4	130 ± 4 (0.4)	130 ± 3	130 ± 4	130 ± 4
Sodium acetate	0.3 ml/min	6	130 ± 3	130 ± 3 (0.8)	130 ± 3	131 ± 3	131 ± 3
Sodium acetate	1.0 ml/min	6	136 ± 4	127 ± 4§ (12.7)	136 ± 4§	137 ± 4	138 ± 3
Sodium chloride	1.0 ml/min	4	141 ± 6	141 ± 5 (1.4)	139 ± 5	138 ± 6	138 ± 5
Sodium bicarbonate	1.0 ml/min	3	124 ± 8	124 ± 9 (0.0)	124 ± 8	124 ± 8	124 ± 7

See table 2 for meaning of symbols.

TABLE 5
Maximal Intrinsic Velocity of Myocardial Contraction, Vmax (sec^{-1})*

		n†	Preinfusion	Infusion			Postinfusion
				Early‡	Middle	Late	
N_2O							
Sodium acetate	0.1 ml/min	6	2.42 ± 0.20	2.44 ± 0.20§ (3.4)	2.42 ± 0.19	2.43 ± 0.20	2.42 ± 0.19
Sodium acetate	0.3 ml/min	6	2.42 ± 0.20	2.48 ± 0.20 (0.1)	2.51 ± 0.20	2.48 ± 0.20	2.50 ± 0.19
Sodium acetate	1.0 ml/min	6	2.48 ± 0.15	2.50 ± 0.15 (4.7)	2.42 ± 0.15	2.45 ± 0.15	2.49 ± 0.15
Sodium chloride	1.0 ml/min	5	2.63 ± 0.23	2.68 ± 0.22 (0.1)	2.66 ± 0.23	2.55 ± 0.22	2.52 ± 0.23
Sodium bicarbonate	1.0 ml/min	3	2.15 ± 0.49	2.19 ± 0.42 (0.0)	2.24 ± 0.42§	2.21 ± 0.39	2.22 ± 0.34
Halothane							
Sodium acetate	0.1 ml/min	6	1.39 ± 0.11	1.39 ± 0.11 (0.1)	1.41 ± 0.11§	1.41 ± 0.11	1.40 ± 0.11
Sodium acetate	0.3 ml/min	6	1.51 ± 0.10	1.52 ± 0.09 (3.1)	1.50 ± 0.10	1.52 ± 0.10	1.52 ± 0.10
Sodium acetate	1.0 ml/min	6	1.47 ± 0.09	1.48 ± 0.09 (3.6)	1.54 ± 0.10	1.50 ± 0.10	1.48 ± 0.09
Sodium chloride	1.0 ml/min	4	1.62 ± 0.07	1.59 ± 0.08 (4.1)	1.55 ± 0.07	1.55 ± 0.08	1.55 ± 0.07
Sodium bicarbonate	1.0 ml/min	3	1.47 ± 0.22	1.43 ± 0.22 (6.0)	1.43 ± 0.22	1.42 ± 0.22	1.44 ± 0.22

See table 2 for meaning of symbols.

tion is whether the intermediary carbohydrate substrates are effective antagonists of halothane-induced myocardial contractile depression in vivo, and therefore potentially useful in man.

To study the direct effects of halothane and acetate on the in vivo heart uninfluenced by reflexes, we produced autonomic blockade with large doses of atropine[6,7] and guanethidine.[5,6,16-18] The predicted plasma level of guanethidine in our dogs was significantly in excess of the level demonstrated to produce complete sympathetic blockade.[19] In preliminary experiments, β-adrenergic blockade was effected with large doses of propranolol. Although control values for the myocardial parameters obtained from these dogs were not noticeably different from those reported in this study, the propranolol-treated animals did not have the level of cardiovascular stability observed in animals given guanethidine. Half of the dogs were also treated with the α-adrenergic blocking drug phenoxybenzamine prior to N_2O anesthesia in order to further stabilize cardiovascular parameters during light levels of anesthesia. There were no significant differences in the results obtained from the phenoxybenzamine-treated and the phenoxybenzamine-untreated experimental subgroups. Slight variations in cardiovascular function were nevertheless seen with alterations of the respiratory cycle, and these were probably due to cyclic changes in cardiac filling.

The concept of the force-velocity relation is well established as an index for the evaluation of changes in myocardial performance during exposure to anesthetics.[20-22] Assessment of this relation in the intact heart requires measurement of both left ventricular pressure and geometry. To eliminate the necessity for geometrical recordings, Shimosato described a method for determining the maximal intrinsic velocity of contraction (V_{max}) in the intact heart.[8] This method is thought to be independent of changes of preload and afterload, and therefore a valid index of myocardial contractility,[23-26] although this is still controversial.[27-29] In Shimosato's method, the first time derivative of isovolumic left ventricular pressure, dP/dt, is divided by KP (K is the coefficient of modulus of elasticity of the series elastic component, its value being 24.7). This value for LVdP/dt/KP (the velocity of shortening of the contractile element) is plotted as a function of P (force per unit area). Because of the early onset of isotonic contraction in the intact heart, LVdP/dt/KP probably never reaches a maximal value. Therefore, the resultant curve is extrapolated back to zero pressure to determine V_{max}, the theoretical velocity of shortening of the unloaded contractile element.

We cannot easily compare Shimosato's V_{max} values[8] with those of our investigation because neither study obtained control values in unmedicated animals. In our study, V_{max} values for 70% N_2O–30% O_2–succinylcholine and 1.4% inspired halothane (balance either O_2 or 70% N_2O in 30% O_2) were approximately 250% and 150%, respectively, greater than the V_{max} of his "control" dogs. The differences may be explained by (1) his administration of chloralose and urethane prior to inhalation anesthesia; (2) our administration of autonomic blocking drugs; and (3) differences in the sequence of electrical filtering. The values obtained in the present study are more comparable to those obtained in human studies.[30]

We also computed another suggested, but less well accepted, index of myocardial contractility, maximal LVdP/dt/KP.[8,23,31,32] The major objection to its use is that maximal LVdP/dt occurs during isotonic contraction.

We have demonstrated that halothane anesthesia depresses LVP, AP, HR, LVdP/dt_{max}, LVdP/dt/KP_{max}, and V_{max} when N_2O-O_2 anesthesia is the "control." During halothane anesthesia, the highest infusion rate of NaAc (1.0 ml/min) depressed LVP, AP, and HR during the initial 4 minutes of the infusion. There was no concomitant alteration of either V_{max} or LVdP/dt/KP_{max}. The depressed recordings returned to control levels within the remaining portion of the infusion period, and both LVP and AP were significantly elevated above control levels in the postinfusion period. This rebound phenomenon cannot be explained by reflex activity because the autonomic blockade was virtually complete. Specific physiologic quantification of the degree of completeness of sympathetic blockade achieved with guanethidine was not performed. No alterations of V_{max} or LVdP/dt/KP_{max} were noted during the postinfusion period. A markedly diminished electrical amplitude of the ECG accompanied the decreased HR. The control infusions of NaCl and $NaHCO_3$ caused no significant changes in the variables studied.

Therefore, acetate did not reverse the depression of myocardial contractility induced

by halothane. Indeed, throughout this study, acetate failed to consistently produce any significant effect on myocardial contractility. Consequently, the hemodynamic effects of acetate—initial depression and rebound elevation of LVP and AP—must have been caused by an effect on the peripheral vasculature. This is in agreement with the well-established vasodilatory properties of acetate.[33-35] One dog not included in this report dramatically demonstrated these vasodilator properties: acetate caused a progressive hypotension eventually leading toward a functional cardiovascular arrest without any alteration in myocardial contractility as measured by V_{max} and $LVdP/dt/KP_{max}$. The acetate-induced depression of the HR and cardiac electrical activity might be related to a direct depression of the sinoatrial node.

Infusions of 0.3 and 1.0 ml/min NaAc consistently raised serum acetate concentrations into the pharmacological range as determined by rat atrial preparations[1] and human therapeutic experiments.[36] Infusion of 1.0 ml/min NaAc and $NaHCO_3$ (both effective sources of buffer base[36-39]) also increased the blood buffer base. The predicted resultant depression of serum potassium[40] was significant only with the NaAc infusion. There was no correlation between alterations in blood buffer base or potassium and cardiovascular parameters.

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NERVE BLOCK FOR PERORAL ENDOSCOPY

Glossopharyngeal and superior laryngeal nerve block anesthesia for peroral endoscopy was performed on 500 patients (313 bronchoscopies, 162 esophagoscopies, and 25 combined bronchoesophagoscopies). The technic allows easy insertion of rigid and flexible scopes or awake tracheal intubation of conscious patients. Glossopharyngeal nerve block causes temporary abolition of the gag reflex together with loss of tactile sensation over the posterior third of the tongue and the lateral and posterior wall of the oropharynx and hypopharynx. Superior laryngeal nerve block results in loss of tactile sensation over the posterior surface of the epiglottis and the mucosa of the larynx and upper trachea.

Ten of the 500 patients (2%) had an inadequate glossopharyngeal block, and 4 of the 313 patients who had a bronchoscopic examination had an inadequate superior laryngeal block. In the remaining patients, excellent anesthesia was obtained with good patient acceptance and minimal morbidity. *(DeMeester TR, Skinner DB, Evans RH, et al: Local nerve block anesthesia for peroral endoscopy. Ann Thorac Surg 24:278-283, 1977)*

Brain Sodium, Potassium, and Osmolality: Effects on Anesthetic Requirement

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We determined the effects of hyperkalemia, hypernatremia, hyperosmolality and hypo-osmolality on halothane requirement (MAC) in dogs. Hyperkalemia did not change cerebrospinal fluid potassium or MAC. Hypernatremia proportionately increased cerebrospinal fluid sodium and osmolality. MAC concomitantly increased 43%. Serum hyperosmolality achieved by administration of 12 and 25% dextrose increased cerebrospinal fluid osmolality without appreciably altering cerebrospinal fluid sodium or MAC. Infusion of 5% dextrose produced hypo-osmolality of blood and cerebrospinal fluid. Cerebrospinal fluid sodium was diluted and MAC was reduced by 24%.

Key Words—POTENCY, anesthetic, MAC. ANESTHETICS, volatile, halothane. IONS, sodium. IONS, potassium. CEREBROSPINAL FLUID, osmolality.

DISEASE or therapeutic intervention may alter body electrolytes and osmolality. Patients with impaired kidney function, dehydration, hyperalimentation, or chronic steroid hormone administration can show considerable changes in serum electrolytes and osmolality. We may impose such changes by IV infusion of salt-free solutions or by irrigation of bladder or stomach with salt-free solutions. Although we prefer to correct electrolyte and osmotic imbalances prior to anesthesia, this is not always possible or desirable.

The excitability of nervous tissue depends in part on the intracellular and extracellular distribution of sodium and potassium.[1] An excess of extracellular potassium causes membrane depolarization. An excess of extracellular sodium causes hyperpolarization. Although hyperpolarization decreases the excitability of the neuron, it results in a larger nerve-action potential and probably a greater release of neurotransmitter at the synapse.[2] A reduction in the nerve-action potential by an increase in extracellular potassium might do the opposite. The relationship between the size of the nerve-action potential and the release of transmitter is such that a 15-mv increase in depolarization produces a tenfold increase in neurotransmitter release.[2] On the other hand, hyperpolarization would decrease the excitability of the postsynaptic membrane adjacent to the subsynaptic membrane and therefore should lead to a block of synaptic transmission.

The foregoing observations suggest that changes in the electrolyte concentrations bathing nerves might influence anesthetic requirements. Indeed, an imbalance of electrolytes has been suggested as causally related to the development of anesthesia.[3]

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Ionic changes (specifically calcium) may affect the phase changes in phosphatidylserine bilayers induced by cyclopropane.[4] Such an influence may be of importance if alteration of nerve-membrane fluidity is the means by which anesthetics exert their effect.[5,6] Anesthetic requirement may be affected by changes in magnesium,[7] calcium (Johnson and Crout, Abstracts of Scientific Papers, American Society of Anesthesiologists Meeting, New York, 1970, p 1), lithium,[8] or bromide.[9]

No reports have indicated the effect of altering the major normal serum ions or serum osmolarity on the dose requirement of general anesthetics. The following report supplies such data. Our results suggest that alterations in brain extracellular sodium may directly affect anesthetic requirement (MAC*).

METHODS

Thirty-three unpremedicated dogs of various ages, breeds, sexes, and weight (mean 23 ± 1 kg) were divided into 6 groups. Anesthesia was induced and maintained with halothane in O_2. A cuffed endotracheal tube was introduced without the use of muscle relaxants, and breathing was controlled with a volume-limited respirator to achieve an end-tidal CO_2 (infrared analysis) of 4 to 5%. Intermittent end-tidal gas samples were obtained from the end of the endotracheal tube via a nylon catheter. Halothane concentration was measured with a Beckman LB-1 infrared analyzer. Esophageal temperature was measured and maintained between 36.5 and 38.5 C by external heating or cooling. MAC was determined as described previously, using tail clamp as the stimulus.[10] All measurements were made after 15 minutes at a constant end-tidal halothane concentration. Arterial blood for blood-gas analysis was drawn from a catheter inserted into the femoral artery. Using a 19-gauge needle, we punctured the cisterna magna at the times indicated below to measure cerebrospinal fluid pressure and to obtain fluid samples for acid-base, osmotic and electrolyte determinations. P_{CO_2} and pH were measured with standard electrodes. Osmolality was determined by the freezing-point technic. Sodium and potassium concentrations in blood and in cerebrospinal fluid were determined by flame photometry. Pressures in the femoral artery and the cisterna magna were transduced with Statham strain gauges and recorded with the ECG on a Grass polygraph.

After induction with halothane, we determined MAC (control) and drew samples of blood and cerebrospinal fluid. In group 1 dogs (6 dogs), we then infused a solution containing 160 mEq/L of potassium chloride.We adjusted the infusion to the maximum permitted by alterations in the ECG and blood pressure. After 3 to 4 hours of infusion and again after 7 to 8 hours of infusion, we redetermined MAC and obtained blood and cisternal fluid.

In a 2nd group (8 dogs), we examined whether changes in sodium altered halothane MAC. A control MAC was determined, and arterial blood and cerebrospinal fluid obtained for analysis. We then administered 10 mEq/kg/hr of a 510 mEq/L sodium chloride (3% NaCl) infusion to which we added 50 mEq/L of sodium bicarbonate and 10 mEq/L of potassium chloride. This solution was infused for 4 hours. Between the 3rd and 4th hour, MAC was redetermined, and blood and cerebrospinal fluid samples again were obtained. After that, 1000 ml of 5% dextrose in H_2O were given IV along with 2000 ml of distilled H_2O instilled into the stomach via an orogastric catheter. After an additional 4 hours, we redetermined MAC, and blood and cerebrospinal fluid samples were drawn.

Next, we examined the influence of changes in serum osmolarity achieved with nonelectrolytes on MAC and cerebrospinal fluid, electrolytes, and osmolality. In the 3rd group (3 dogs), we determined a control MAC and took arterial blood and cerebrospinal fluid samples. Then 4 g/kg/hr of mannitol were infused for 4 hours. MAC was redetermined in the 4th hour of infusion, and arterial blood and cerebrospinal fluid again were obtained for analysis.

In the 4th group (6 dogs), after the determination of a control MAC and electrolytes and osmolality in serum and cerebrospinal fluid, 500 ml/hr of 25% dextrose were infused for 3 hours. MAC was redetermined in the 3rd hour, and blood and cerebrospinal fluid obtained.

In the 5th group (5 dogs), we determined a control MAC, and took blood and cerebrospinal fluid samples. Then 1000 ml/hr of

*MAC is the minimum alveolar concentration of anesthetic required to abolish movement in response to a painful stimulus in 50% of animals. It is an anesthetic ED_{50} which ordinarily is unaffected by a variety of factors, including duration of anesthesia.[10]

12% dextrose were infused for 4 hours and MAC redetermined in the 4th hour. Blood and cerebrospinal fluid analyses were obtained after redetermination of MAC.

In the 6th group (5 dogs), a control MAC was determined and blood and cerebrospinal fluid samples were drawn. We then administered 1000 ml/hr of 5% dextrose for 4 hours. MAC was redetermined, and blood and cerebrospinal fluid again were obtained during the 4th hour of infusion.

Paired or unpaired Student's *t*-tests were used to determine the significance of changes seen in MAC, electrolytes, and osmolality in serum and cerebrospinal fluid. A p value of less than 0.05 was accepted as significant.

RESULTS

Group 1 (Potassium Infusion) — Serum potassium increased both at the 4th and the 8th hour of infusion (table). Cerebrospinal fluid potassium increased significantly but the increase was slight (11% at 8 hours compared to a 95% increase in serum). As might be expected, MAC did not change.

Group 2 (Hypertonic Saline Infusion)— Cerebrospinal fluid sodium increased 31 mEq/L (25%) in parallel with a 36 mEq/L increase in blood sodium. At the same time, cerebrospinal fluid potassium and osmolality increased 37 and 20%, respectively. The associated 43% increase in MAC was significant. Infusion of 5% dextrose accompanied by intragastric instillation of distilled H_2O eliminated all significant differences that had appeared at 3 to 4 hours. Note that n equals 5 for this group and that therefore the control values are slightly different from those listed under control in the table.

Group 3 (Mannitol Infusion)—Although serum sodium decreased 10 mEq/L, cerebrospinal fluid sodium, potassium, osmolality, and MAC significantly increased, by about the same amount as in group 2.

Group 4 (25% Dextrose Infusion)—Serum sodium decreased 14 mEq/L while cerebrospinal fluid osmolality increased significantly (60 m osm, as in group 2). Cerebrospinal fluid sodium rose slightly. MAC was not significantly increased.

Group 5 (12% Dextrose Infusion)—Serum osmolality increased and serum sodium decreased significantly but neither cerebrospinal fluid sodium nor MAC was changed. Cerebrospinal fluid osmolality increased significantly.

Group 6 (5% Dextrose Infusion)—MAC and serum and cerebrospinal fluid sodium and osmolality decreased significantly.

In the 3rd through 6th groups a serum metabolic acidosis was present, probably secondary to dilution of serum base. This acidosis was not reflected in the cerebrospinal fluid. Cerebrospinal fluid acid-base status did not change significantly in any group.

DISCUSSION

Cerebrospinal fluid more closely represents brain extracellular fluid than plasma and hence we have emphasized the correlates of MAC with ionic changes in cisternal fluid. The blood-brain barrier appears to prevent alterations in some cerebrospinal fluid ions. Thus, in our experiment the serum potassium nearly doubled but cerebrospinal fluid potassium changed only slightly. That potassium does not easily cross the cerebrospinal fluid-brain barrier has been observed by other workers.[11-13] As might be expected, in the absence of spinal fluid changes, MAC did not change with hyperkalemia. Cerebrospinal fluid potassium did change with other treatments. Both 12 and 25% dextrose infusions, mannitol infusion, and hypertonic saline infusion were associated with an increase in potassium. However, only the hypernatremia-associated increase in potassium altered MAC (table, fig 1).

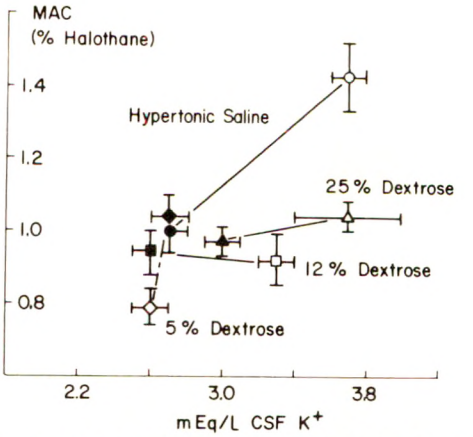


FIG 1. The correlation of changes in MAC with change in cerebrospinal fluid (CSF) potassium applied only to the results obtained with infusion of hypertonic saline (hypernatremia) or mannitol (see table for mannitol data). Hypertonic (12 or 25%) dextrose infusions increased potassium without altering MAC while 5% dextrose infusion decreased MAC without altering potassium. The bars at each point indicate the standard error for MAC and for potassium. The closed symbols indicate control values while the open symbols indicate the associated test values.

TABLE
Summary of Results

		Control				Test							
						4th hour				8th hour ($n = 5$)			
		Na^+	K^+	Osm	MAC	Na^+	K^+	Osm	MAC	Na^+	K^+	Osm	MAC
Group 1 Hyperkalemia ($n = 6$)	Blood	148 ± 1	3.8 ± .2	—	1.09 ± .04	140 ± 2*	6.8 ± .2*	—	1.07 ± .05	140 ± 3*	7.4 ± .5	—	1.09 ± .04
	CSF	148 ± 1	2.5 ± .1	—		143 ± 3	2.6 ± .1*	—		142 ± 3	2.7 ± .1*	—	
										Recovery ($n = 5$)			
Group 2 Hypertonic saline ($n = 8$)	Blood	143 ± 2	3.7 ± .2	299 ± 2	1.00 ± .06	179 ± 4*	4.8 ± .5*	373 ± 8*	1.43 ± .10*	148 ± 2	3.2 ± .1	312 ± 9	1.02 ± .14
	CSF	149 ± 2	2.7 ± .1	302 ± 2		181 ± 3*	3.7 ± .1*	361 ± 7*		161 ± 2	3.3 ± .3	328 ± 10	
Group 3 Mannitol ($n = 3$)	Blood	138 ± 3	4.4 ± .2	301 ± 7	1.13 ± .08	123 ± 3*	4.5 ± .5	398 ± 4	1.49 ± .10*				
	CSF	147 ± 2	2.7 ± .1	300 ± 4		176 ± 4*	3.7 ± .1*	379 ± 6*					
Group 4 25% D/W ($n = 6$)	Blood	147 ± 3	3.9 ± .2	301 ± 2	.07 ± .04	133 ± 2*	3.8 ± .5	370 ± 14	1.04 ± .04				
	CSF	154 ± 1	3.0 ± .1	302 ± 3		166 ± 3*	3.7 ± .3*	359 ± 10*					
Group 5 12% D/W ($n = 5$)	Blood	147 ± 2	3.7 ± .1	306 ± 6	.95 ± .07	106 ± 1*	4.9 ± .4	358 ± 10*	.92 ± .07				
	CSF	150 ± 2	2.6 ± .1	305 ± 4		155 ± 2	3.3 ± .1*	346 ± 8*					
Group 6 5% D/W ($n = 5$)	Blood	146 ± 2	3.7 ± .3	301 ± 4	1.04 ± .06	119 ± 3*	4.0 ± .2	271 ± 5*	.79 ± .05*				
	CSF	151 ± 2	2.7 ± .1	302 ± 2		133 ± 3*	2.6 ± .1	276 ± 3*					

*Significantly different from control. "Control" refers to values plus or minus the standard error obtained before infusions began, while "test" refers to values obtained 3 to 4 hours following the start of infusion and, in the case of groups 1 and 2, 7 to 8 hours following the start of infusion. Electrolytes are mEq/L, Osm is mOsm/L, and MAC is percent halothane.

Liley reported that an increase in osmotic pressure increased the frequency of spontaneous discharges at the neuromuscular junction.[13] This suggests that hyperosmolality increases nervous irritability and neurotransmitter discharge. Thus, a change in osmolality might influence anesthetic requirement. To distinguish between osmolality and sodium changes as the cause of the change in MAC, we tried to change osmolality independently of sodium by infusing dextrose or mannitol. The success of this approach was determined by the ability of mannitol and dextrose to cross the blood-brain barrier.

One group of workers has suggested that an infusion of 4 g/kg/hr of mannitol for 4 hours injures the cerebrospinal fluid-brain barrier and allows mannitol to cross into the cerebrospinal fluid.[14] Our results do not confirm this suggestion. Cerebrospinal fluid osmolality in group-3 dogs increased significantly, but the increase in cerebrospinal fluid sodium coupled with the associated negatively charged ions explains the osmolality change. In any event, since both sodium and osmolality increased, we could not estimate their relative effect on MAC.

Although there is some limitation to the passage of dextrose into cerebrospinal fluid, the limitation is only partial.[15] We found (data not shown) that the cerebrospinal fluid dextrose equaled about 30% of the plasma concentration. Administration of either 25 or 12% dextrose (group 4 and 5) increased cerebrospinal fluid osmolality with either small (group 4) or no (group 5) increases in cerebrospinal sodium (table, fig 2). MAC did not change remarkably in either group. Administration of 5% isotonic dextrose (group 6) reduced both cerebrospinal fluid sodium and osmolality. This dilution of cerebrospinal fluid sodium was associated with a reduction in MAC. Thus, in conflict with what might be predicted from Liley's work, our results suggest that changes in osmolality do not exert a major effect on anesthetic requirement.

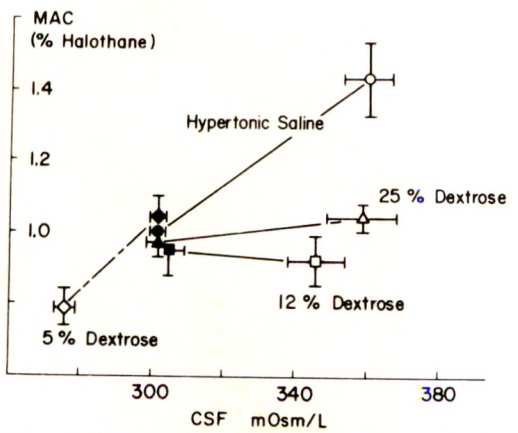


FIG 2. MAC correlated with the increase in osmolarity caused by hypertonic saline infusion or the decrease in osmolarity associated with 5% dextrose infusion. Administration of 12 or 25% dextrose increased osmolarity without increasing MAC.

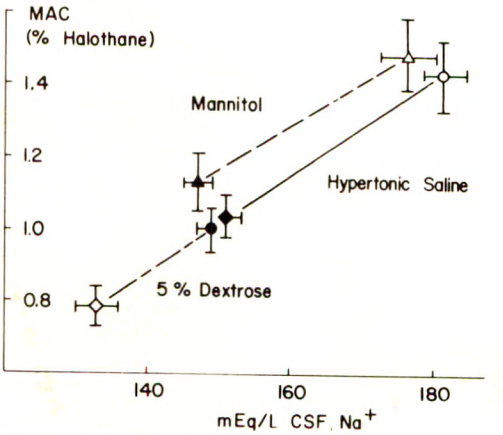


FIG 3. MAC consistently increased with an increase in cerebrospinal fluid sodium and decreased with a decrease in sodium.

Sodium does cross the cerebrospinal-brain barrier.[16-19] Hypernatremia probably increased cerebrospinal fluid sodium not only by sodium crossing the blood-brain barrier, but also by dehydration secondary to administration of hyperosmotic solutions. Dehydration is reflected in the concomitant cerebrospinal fluid potassium and osmolality increase. The increased MAC in group 2 correlated well with cerebrospinal fluid sodium (table, fig 3). The correlation of anesthetic requirement with changes in cerebrospinal fluid sodium also extended to the infusions of mannitol and 5% dextrose (table, fig 3). Infusion of 25% dextrose produced a small (12 mEq/L) but significant increase in sodium. The associated small increase in the average MAC (0.07% halothane) was not significant. The other infusions produced changes in sodium and MAC that were too small to discern associated alterations (table).

Our data suggest that changes in serum electrolytes or osmolality may be associated with changes in anesthetic requirement when they induce changes in brain sodium. Thus, many fluids that we (5% dextrose in H_2O, hypertonic saline, 5% dextrose in lactated Ringer's solution) or our surgical colleagues

(mannitol, distilled H_2O for transurethral resection or gastric lavage) give may alter anesthetic requirement. In the same way, disease states which increase or decrease cerebrospinal fluid sodium (eg, dehydration, diabetes insipidus) may alter anesthetic requirement.

The relationship of MAC with sodium may be of theoretical interest. One explanation may be found in the work of Finck, Ngai, and Berkowitz.[20] They suggested that anesthetics may act in part or whole by releasing enkephalin, a naturally occurring opiatelike substance found in both brain and spinal cord. Indeed they found that the administration of naloxone increased anesthetic requirement for a number of inhaled agents. The connection with sodium comes from the demonstration that sodium inhibits the binding of opiates to opiate receptors in the brain and thereby presumably interferes with the action of both endogenous and exogenous narcotics.[21] However, this effect of sodium is shared by lithium,[22] and we have found (unpublished data) that lithium administration decreases MAC.

Another explanation may lie in the potential effect of sodium on transmitter release. As noted earlier, it is known that an increase in extracellular sodium increases the transmembrane potential and the nerve action potential.[1] Diamond, Havdala, and Sabelli demonstrated that an increase in extracellular sodium antagonizes the depression of the nerve action potential produced by enflurane, halothane, or ketamine.[23] Release of neurotransmitter is directly related to the size of nerve action potential.[2] This suggests the possibility of a competitive effect of anesthesia and sodium at the nerve terminal. Diamond's group also found that the threshold for depolarization was lowered by an increase in sodium.[23] They demonstrated that the blockade of nervous transmission produced by halothane, enflurane, or ketamine at low sodium concentrations could be antagonized by raising the sodium concentration. Such an antagonism might apply both to the nerve terminal and to the postsynaptic membrane.

The work of Shrivastav and his associates also may be pertinent to our findings. They found that trichloroethylene[24] or ketamine[25] may decrease the peak of the nerve action potential by increasing resting sodium permeability and hence intracellular sodium. As suggested in the introduction, this might impair transmitter release. A difficulty in the interpretation of the importance of Shrivastav's work is that the concentrations of anesthetic used were well beyond those required for anesthesia.

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MYOCARDIAL CHANGES IN MALIGNANT HYPERTHERMIA

Although considerable information is available about the structural and biochemical changes in the skeletal muscles of patients with malignant hyperthermia, little is known of the cardiac changes in this disease. However, ventricular fibrillation and cardiac arrest occur frequently. In 3 patients with malignant hyperthermia, contraction bands and foci of myofiberlysis were found in the heart at necropsy. Ultrastructurally, areas of myofiber overstretching adjacent to contraction bands and foci of extensive myofiberlysis were associated with disruptions of the sarcolemma. Similar ultrastructural findings were seen in the skeletal muscles of these patients and may be responsible for the hyperkalemia which is a constant feature of malignant hyperthermia. The ventricular arrhythmias frequent in this disease are likely the result of direct damage to cardiac muscle rather than secondary to elevated plasma levels of potassium. *(Fenoglio JJ Jr, Irey NS: Myocardial changes in malignant hyperthermia. Am J Pathol 89:51-58, 1977)*

Anesthetic Requirements and Cardiovascular Effects of Fentanyl-Oxygen and Fentanyl-Diazepam-Oxygen Anesthesia in Man

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The cardiovascular effects of anesthetic doses of IV fentanyl (up to 50 μg/kg) and these doses of fentanyl plus diazepam (10 mg) were determined in 23 patients breathing O_2 prior to mitral valvular replacement. Fentanyl was administered IV at 50 to 200 μg/min until the patients were unresponsive to verbal command and pinprick stimulation of the chest. Succinylcholine was then administered, the trachea intubated, respirations controlled to maintain P_{aCO_2} between 30 and 35 torr, and additional fentanyl given until each patient had received 50 μg/kg of fentanyl. Following this, 10 patients received diazepam (10 mg IV) over a 20-second period. Cardiovascular data were recorded before and after every 10 μg/kg of fentanyl (up to 50 μg/kg) and 2, 4, 6, and 8 minutes after diazepam. During the ensuing operation additional fentanyl was administered whenever blood pressure or heart rate increased 15% or more above preanesthetic values.

Unresponsiveness was achieved with an average of 11 ± 3 μg/kg of fentanyl. Patients receiving fentanyl alone required total doses of 74 ± 10 μg/kg fentanyl for the entire operation, while those given fentanyl plus diazepam needed 69 ± 9 μg/kg fentanyl. Fentanyl (20 μg/kg) decreased heart rate and arterial blood pressure but did not significantly change stroke volume, cardiac output, central venous pressure, or peripheral arterial resistance. Additional fentanyl did not further alter heart rate or arterial pressure nor change any other variable measured. Addition of diazepam after fentanyl decreased stroke volume, cardiac output, blood pressure, and peripheral resistance and increased central venous pressure but did not alter heart rate.

These data demonstrate that anesthetic doses of fentanyl and O_2 produce minimal changes in cardiovascular dynamics but that addition of diazepam after large doses of fentanyl results in cardiovascular depression. Our findings suggest that fentanyl-O_2 anesthesia may be an attractive alternative to morphine anesthesia in patients with little cardiac reserve.

Key Words — ANESTHETICS, intravenous, fentanyl. ANALGESICS, narcotic, fentanyl. ANESTHESIA, cardiovascular.

FENTANYL, in doses of 10 μg/kg, produces few circulatory changes in man[1] and, in doses of 20 μg/kg, has little effect on left ventricular dynamics in blood-perfused dog hearts.[2,3] Large doses of fentanyl (0.05 to 2.0 mg/kg) plus O_2 result in little alteration of circulatory dynamics in the intact dog and produce anesthesia adequate for thoracotomy.[4] On the basis of these studies, we and a number of other clinicians have been routinely using high-dose (50 to 100 μg/kg) fentanyl and O_2 or fentanyl, diazepam, and O_2 as "complete" anesthetics in open-heart operations. However, the cardiovascular effects of these large doses of fentanyl have not been investigated in man. In this study we measured the cardiovascular effects of anesthetic doses of fentanyl (up to 50 μg/kg) during O_2 breathing and the effects of 50 μg/kg of fentanyl plus 10 mg of diazepam in 23 patients about to undergo mitral valvular replacement operations.

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METHODS

Written informed consent was obtained from each of the patients at the time of the preoperative visit. All patients were premedicated with pentobarbital (60 to 100 mg) and atropine (0.3 to 0.5 mg), IM, 90 minutes before the scheduled operation.

Prior to anesthesia, an IV line was established in an upper extremity, a central venous pressure catheter was placed percutaneously into the right atrium from the antecubital fossa or neck, and a radial or brachial artery catheter was inserted percutaneously and threaded 30 to 72 cm into the central aorta. The aortic pressure catheter was attached via an arterial pressure transducer to a central digital computer substation in the operating room. After appropriate dye dilution calibration as previously described,[5] Warner's method of analyzing the central aortic pulse-pressure curve was used to determine cardiac output, stroke volume, arterial blood pressure, and peripheral arterial resistance.[5]

With the patient breathing pure O_2 for a minimum of 15 minutes, fentanyl was administered IV at a rate of 50 to 100 μg/min for the first 4 minutes and 150 to 200 μg/min thereafter until the patients were unresponsive to verbal command and pinprick stimulation of the chest. Respirations were first assisted, and then controlled. Succinylcholine (1.5 mg/kg IV) was then given and the trachea intubated. Respiration was controlled to maintain $Paco_2$, as measured in aortic blood every 15 to 30 minutes, between 30 and 35 torr. After intubation, additional fentanyl was administered (at a rate of 150 to 200 μg/min) until each patient had received 50 μg/kg. Following this, 10 of the patients received diazepam (10 mg IV) over a 20-second period.

Cardiovascular data were recorded before and after 5 and 10 μg/kg of fentanyl and thereafter following every 10 μg/kg of the compound. Data were also recorded 2, 4, 6, and 8 minutes after diazepam. The surgical procedure began immediately after completion of the study. During operation, increments of pancuronium (1 to 3 mg IV) were given as necessary. Additional fentanyl was administered at a rate of 200 μg/min whenever mean arterial blood pressure, heart rate, or cardiac output increased 15% or more above preanesthetic (control) values.

RESULTS

Duration of operation was similar in the 2 groups and averaged 323 ± 37 minutes in patients receiving only fentanyl and 336 ± 41 minutes in patients receiving fentanyl and diazepam. Patients became unresponsive to verbal command and pinprick stimulation after an average of 660 ± 189 μg fentanyl (11 ± 3 μg/kg, range 8 to 15 μg/kg). Administration of succinylcholine and intubation at this time did not significantly change any cardiovascular variable measured. Patients receiving fentanyl and O_2 alone required an average total dose of 4510 ± 512 μg of fentanyl (74 ± 10 μg/kg) while those given fentanyl plus diazepam and O_2 needed 4290 ± 441 μg fentanyl (69 ± 9 μg/kg) for the entire operation.

Fentanyl (5 and 10 μg/kg) did not significantly change any cardiovascular variable studied (table). Fentanyl (20 μg/kg) produced a significant reduction of heart rate and mean arterial blood pressure but did not significantly change stroke volume, cardiac output, central venous pressure, or peripheral arterial resistance. Additional fentanyl, up to 50 μg/kg, did not further alter heart rate or arterial blood pressure nor change any other variable measured. Administration of diazepam after fentanyl decreased stroke volume, cardiac output, mean arterial blood pressure, and peripheral arterial resistance and increased central venous pressure but did not alter heart rate. The latter changes were maximal 4 minutes after administration of diazepam but still present after 8 minutes.

In no instance was there rigidity of the chest wall or difficulty in ventilation at any time during anesthetic induction or throughout the operative procedure. When questioned postoperatively, no patient experienced pain during operation or remembered any aspect of tracheal intubation or operation.

DISCUSSION

Large doses of IV morphine (0.5 to 3.0 mg/kg) plus O_2 produce little change in myocardial mechanics in isolated heart preparations and in cardiovascular dynamics in intact, supine man.[6] As a result, morphine has become popular as a supplementary or complete anesthetic in patients with marginal cardiac reserve.[7-9] Incomplete anesthesia,[7] hypotension,[7,8] increased blood requirements,[9] antidiuresis,[10] and cardiovascular depression when combined with N_2O[11]

TABLE

Cardiovascular Effects of Large Doses of Fentanyl and Fentanyl Plus Diazepam (Mean ± SD)

		Fentanyl dosage (μg/kg)						Minutes after 10 mg diazepam			
	Control	5	10	20	30	40	50	2	4	6	8
Heart rate (beats/min)	67 ±8	63 ±7	59 ±7	55* ±6	55* ±6	57* ±6	57* ±7	59 ±8	60 ±8	59 ±7	58 ±8
Stroke volume (ml)	51 ±8	52 ±8	54 ±8	56 ±9	54 ±8	56 ±9	58 ±9	48‖ ±6	46‖ ±5	50§ ±6	51§ ±6
Cardiac output (L/min)	3.4 ±0.5	3.3 ±0.5	3.2 ±0.4	3.1 ±0.4	3.0 ±0.4	3.2 ±0.5	3.4 ±0.4	2.8*‖ ±0.3	2.7*‖ ±0.3	2.9§ ±0.4	2.9§ ±0.4
Peripheral arterial resistance (PRU)	23.8 ±1.2	22.7 ±1.1	22.5 ±1.1	22.2 ±1.1	22.0 ±1.1	21.8 ±1.2	21.2 ±1.2	20.3* ±1.2	18.1†§ ±1.3	18.6†§ ±1.2	19.1†§ ±1.2
Mean arterial pressure (torr)	89 ±8	83 ±9	80 ±8	78* ±7	76* ±7	78* ±7	77* ±8	69†§ ±9	61‡‖ ±8	66†§ ±7	67‡§ ±8
Central venous pressure (torr)	6 ±2	5 ±2	5 ±2	6 ±2	7 ±2	7 ±2	7 ±2	11*§ ±2	11*§ ±2	11*§ ±2	10*§ ±2

*$p<0.05$, †$p<0.025$, ‡$p<0.01$, Student's paired t-test when compared to control values

§$p<0.05$, ‖$p<0.025$, Student's paired t-test when compared to values following 50 μg/kg fentanyl

have been demonstrated as problems associated with morphine anesthesia. Fentanyl also produces little change in myocardial mechanics.[2,3] Analgesic doses of fentanyl in man (10 μg/kg)[1] and anesthetic doses in the dog (0.05 to 2.0 mg/kg)[4] cause minimal alterations in cardiovascular dynamics. As a result, large doses of fentanyl, as the sole anesthetic, plus O_2 have been suggested as an anesthetic technic for patients with poor myocardial function.[4] However, the anesthetic requirements and cardiovascular effects of fentanyl as the sole anesthetic have not been carefully studied in man.

The results of this investigation demonstrate that 8 to 15 μg/kg of IV fentanyl when used as the sole anesthetic produces unconsciousness and avoids any changes in cardiovascular dynamics during induction and intubation in patients with mitral valvular disease. Our data also indicate that additional fentanyl up to 50 μg/kg results in small decreases in heart rate and arterial blood pressure but no significant changes in stroke volume, cardiac output, or peripheral arterial resistance. However, addition of diazepam after large doses of fentanyl produces significant cardiovascular depression.

In a previous study in dogs, Liu and coworkers[4] showed that the most significant alteration in cardiovascular dynamics produced by large doses of fentanyl was a reduction in heart rate. Similar, though less marked decreases in heart rate were found in this study. We (W. S. Liu, unpublished data) and others[12] have shown that bradycardia after fentanyl can be significantly decreased by premedication with atropine and totally abolished by surgical vagotomy. This suggests that, as with morphine, bradycardia after fentanyl is secondary to stimulation of the vagal nucleus in the medulla. Atropine was used as a premedicant in this study; however, recent work in dogs and man (W. S. Liu and T. H. Stanley, unpublished data) suggest that slow administration of fentanyl, particularly during anesthetic induction, can markedly reduce the degree of bradycardia in the absence of atropine premedication. Slow administration of fentanyl during anesthetic induction also decreases the incidence of chest-wall rigidity, a complication that was not seen in this study but which has been reported by others[13] after fentanyl.

Diazepam (5 to 10 mg) has little effect on cardiovascular dynamics in unanesthetized patients with cardiac disease.[14] Because of this and its well-known amnesic effects diazepam has been advocated as a supplement during anesthetic technics employing IV agents.[15,16] In a previous report[16] we showed that diazepam (5 and 10 mg, IV) produced only modest decreases in heart rate and arterial blood pressure and a small increase in peripheral arterial resistance when administered after 2 mg/kg of morphine in patients with a variety of cardiac lesions about to undergo open-heart surgery. Depression of the cardiovascular system after diazepam was more marked in the present study. Cardiac output and mean arterial blood pressure were reduced 18 and 22% respectively, when compared to control, and 18 and 10% when compared to values following 50 μg/kg of fentanyl. Since diazepam reduced stroke volume and peripheral arterial resistance and simultaneously increased central venous pressure, the data suggest that diazepam acts as a direct myocardial depressant when given after large doses of fentanyl.

In a group of patients similar to those studied in this investigation and also undergoing mitral valve operations, we showed that 1.5 ± 0.4 mg/kg of morphine (as the sole anesthetic) was required for the entire operation.[17] In those patients, an average of 0.4 ± 0.2 mg/kg of morphine produced unconsciousness and no response to pinprick. These data when compared to our findings in the present study suggest that fentanyl is 20 to 40 times more potent than morphine when used as a complete or sole anesthetic. In contrast to our patients receiving morphine for mitral valve operations, who had significant increases in heart rate and blood pressure on intubation, our patients receiving fentanyl in this study sustained no change in these or in any other cardiovascular variable measured on intubation. Absence of change in cardiovascular dynamics, particularly of heart rate, in a patient with obstruction to ventricular filling is a desirable finding. However, it also suggests that patients in our present study were more deeply anesthetized than patients in our former study and that fentanyl, in anesthetic doses, may be even more than 40 times as potent as morphine.

When used as the sole anesthetic, morphine results in increased blood requirements during bypass, during the entire operation, and during the first 24 hours postoperatively when compared to halothane-O_2 anesthesia. This has been attributed to the venodilating property of the compound and

has been considered a serious disadvantage of morphine anesthesia. Venodilation and increased blood requirements have not been noted after large doses of fentanyl (Stanley, unpublished data). Indeed, there are data which suggest that fentanyl increases venous tone and decreases venous compliance.[18]

Computation of cardiac output, stroke volume, and peripheral arterial resistance via computer analysis of the central aortic pulse contour as described by Warner and coworkers has been criticized by some as being inaccurate.[19,20] Over 10 years ago Warner and coworkers demonstrated, in unanesthetized man and dogs, that pulse contour computed cardiac output is closely correlated (r = 0.96 to 0.98) with cardiac output measured using dye-dilution and electromagnetic flowmeter methods during rest and exercise and during infusion of metaraminol, atropine, or neostigmine.[21,22] In a recent study, English and coworkers showed that pulse contour computed cardiac output is closely correlated (r = 0.95) with thermodilution measured cardiac output in halothane-anesthetized dogs over a range of cardiac output of 0.5 to 4.0 L/min for up to 8 hours after initial calibration (J. English, T. H. Stanley, M. Hodges, et al, unpublished data). Furthermore, English's work demonstrated that correlation of thermodilution and pulse contour measured cardiac output remains good (r = 0.80 or better) during conditions of changing peripheral arterial resistance (with infusions of norepinephrine or nitroprusside) as long as computer-calculated peripheral resistance is within 50% of initial calibrated values. When peripheral resistance is changed, more than 50% of initial calibrated values correlation falls off. These findings in dogs are consistent with observations made in man anesthetized with a variety of anesthetics and subjected to alterations in cardiac output (measured with thermodilution and pulse contour methods), with or without simultaneous changes in peripheral arterial resistance (T. H. Stanley, unpublished data).

A legitimate criticism of the findings in this study could be that they were made in patients with mitral stenosis. Increases in cardiac output or stroke volume in response to fentanyl would be unlikely in patients with mitral stenosis, though increases might be observed in cardiovascularly normal patients under similar circumstances. Additional studies in our operating rooms (T. H. Stanley, unpublished data) have demonstrated that patients without cardiovascular disease experience similar changes in cardiovascular dynamics during high-dose fentanyl-oxygen anesthesia, as do patients with mitral stenosis.

In conclusion, our findings in this study demonstrate that large doses of fentanyl, as the sole anesthetic, with O_2 produce complete anesthesia and minimal changes in cardiovascular dynamics in patients with mitral valvular disease. They also indicate that addition of diazepam after large doses of fentanyl results in significant cardiovascular depression. Fentanyl-O_2 anesthesia is an attractive alternative to morphine in patients with little cardiac reserve.

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PREVENTION OF NITROPRUSSIDE TOXICITY

To investigate the role of hydroxocobalamin in prevention of cyanide intoxication during infusion of sodium nitroprusside, two groups of patients were studied. Group 1 received nitroprusside alone, while group 2 received nitroprusside and hydroxocobalamin. Total nitroprusside dose per patient was 44.1 ± 12.3 mg (mean ± SE) (0.61 ± 0.17 mg/kg) in group 1 and 44.6 ± 10.5 (0.65 ± 0.17 mg/kg) in group 2 ($p>0.05$). Red-cell and plasma cyanide levels were 83.44 ± 23.12 and 3.51 ± 1.01 μg per 100 ml after nitroprusside alone and were 33.18 ± 17.29 and 2.18 ± 0.65 μg per 100 ml after nitroprusside plus hydroxocobalamin. Metabolic acidosis developed in patients with red-cell cyanide levels higher than 75 μg per 100 ml. When hydroxocobalamin infusion was stopped before sodium nitroprusside infusion was discontinued, blood cyanide levels and base deficit increased in a manner similar to that in the untreated group. These data show that hydroxocobalamin prevents cyanide transfer from red cells and plasma to tissue after nitroprusside metabolism, and thereby decreases cyanide toxicity from large IV doses of nitroprusside. *(Cottrell JE, Casthely P, Brodie JD, et al: Prevention of nitroprusside-induced cyanide toxicity with hydroxocobalamin. N Engl J Med 298:809-811, 1978)*

Acute and Chronic Changes in Intra- and Extracellular Potassium and Responses to Neuromuscular Blocking Agents

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The effects of acutely induced metabolic and respiratory alkalosis with reduction of serum potassium concentration as well as chronic total body potassium depletion induced by furosemide treatment were evaluated and correlated with alteration of neuromuscular blockade induced by d-tubocurarine, pancuronium, and succinylcholine in 12 mongrel dogs. Acute respiratory and metabolic alkalosis significantly reduced serum potassium by about 26%, while chronic furosemide treatment (1 mg/kg IV daily for 14 ± 4 days) significantly reduced both serum potassium concentration (4.16 ± 0.31 to 3.27 ± 0.14 mEq/L) and skeletal muscle potassium content (80.9 ± 5.6 to 58.7 ± 4.1 mEq/kg).

Succinylcholine neuromuscular blockade was essentially unchanged by acute respiratory or metabolic alkalosis or by chronic furosemide treatment, except for more rapid onset of blockade when 0.1 mg/kg succinylcholine was administered during metabolic alkalosis. Acute respiratory alkalosis shortened the duration of neuromuscular blockade induced by d-tubocurarine and pancuronium while acute metabolic alkalosis shortened the duration of pancuronium only and had no effect on d-tubocurarine. Chronic furosemide treatment had no effect on either d-tubocurarine or pancuronium neuromuscular blockade.

Potassium concentration gradients between the intracellular and the extracellular compartments may be more important than cellular potassium depletion per se in affecting responses to neuromuscular blocking agents such as succinylcholine, d-tubocurarine, or pancuronium. Serum alkalemia and hypokalemia antagonize the duration of the neuromuscular blocking action of d-tubocurarine and pancuronium but not that of succinylcholine.

Key Words—IONS, potassium. NEUROMUSCULAR RELAXANTS, d-tubocurarine. NEUROMUSCULAR RELAXANTS, pancuronium. NEUROMUSCULAR RELAXANTS, succinylcholine.

It is generally accepted that acute respiratory alkalosis antagonizes the neuromuscular blockade induced by d-tubocurarine and pancuronium bromide, while succinylcholine blockade is believed to be potentiated.[1-5] While no previous studies have related changes in serum potassium levels with changes in neuromuscular blocking agent activity, it is known that pH changes induce alteration of serum potassium levels.[6] Therefore, this study attempts to define the effects of acute extracellular hypokalemia and chronic (intra- and extracellular) potassium deficiency on neuromuscular blocking agent activity in the dog. Neuromuscular blocking agents evaluated were d-tubocurarine, pancuronium, and succinylcholine.

METHODS

Twelve healthy male mongrel dogs (16.2 to 23.1 kg) served as the experimental subjects. The animals were divided into 3

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groups of 4 animals, each group receiving 2 IV doses of a single neuromuscular blocking agent: d-tubocurarine chloride, 0.1 mg/kg and 0.15 mg/kg; pancuronium bromide, 0.01 mg/kg and 0.015 mg/kg; and succinylcholine chloride, 0.03 mg/kg and 0.1 mg/kg. Methods used for measurement of neuromuscular blockade have been previously described.[7] Briefly, anesthesia was induced with IV thiopental (25 mg/kg), the trachea intubated, and the lungs mechanically ventilated with 1% halothane in 60% N_2O and O_2. Arterial P_{CO_2} was maintained between 34 and 38 torr.

After immobilization of a hind leg, the peroneal nerve was stimulated percutaneously via needle electrodes by a Grass nerve stimulator at 0.6 Hz, 1.5-msec duration and with voltage twice threshold (40 to 60 V). A Grass FT-10 force-displacement transducer was connected to a hind paw by an inflexible steel wire and the twitch tension recorded on a Model 5 Grass polygraph. Indices of neuromuscular blockade measured were (1) latency (time from initial decrease in twitch tension to maximal blockade); (2) maximal twitch-height depression; and (3) the time required for return to 90% of control twitch tension. Forty-five minutes were allowed between doses of the neuromuscular blocking agent in each dog.

Each animal was studied 4 times: under control conditions (arterial P_{CO_2} 34 to 38 torr), during acute respiratory alkalosis, during acute metabolic alkalosis, and after 14 ± 4 days of daily furosemide treatment (1 mg/kg IV). An average of 7 days was allowed between each of the first 3 study periods. Acute respiratory alkalosis (arterial P_{CO_2} between 20 and 25 torr) was brought about by increasing inspiratory tidal volume and/or rate. Acute metabolic alkalosis was induced by an IV infusion of sodium bicarbonate in amounts (4 to 8 mEq/kg) adequate to elevate arterial pH to 7.50-7.60. Chronic hypokalemia was induced by administration of furosemide, 1 mg/kg IV, daily for 14 ± 4 days. Serum electrolytes were measured at 3-day intervals during daily furosemide. Following the final study period, the animal was sacrificed, and 3 muscle specimens weighing approximately 1 g were excised from the hind leg for determination of tissue sodium and potassium content. Blood-gas determinations were performed on an ABL-1 automated analyzer. Serum and tissue electrolytes were measured by an IL-143 flame photometer.

Technic of Muscle Electrolyte Determination—Triplicate samples of hind limb skeletale muscle of approximately 1 g were digested in micro-Kjeldahl tubes with 4 ml of 50% H_2SO_4 and 3 ml 30% H_2O_2 for approximately 40 minutes until the tissue was completely dissolved. The liquified mixture was filtered to eliminate fat residue and diluted to 20 ml with distilled H_2O. Sodium and potassium contents were then measured by an IL-143 flame photometer. Tissue electrolyte content was calculated by the formula:

$$\text{mEq/kg} = \text{mEq/1000 cc (IL reading)} \times \text{dilution volume (cc)} \times \frac{1}{\text{tissue wt (g)}}$$

RESULTS

No significant differences among the 3 groups were observed in control arterial blood-gas tensions, arterial pH, or serum sodium or potassium concentrations. Acute respiratory alkalosis caused significant reduction of arterial P_{CO_2} and serum potassium and elevation of arterial pH, but no change in serum sodium (table 1). Infusion

TABLE 1
Effects of Acute Respiratory Alkalosis, Acute Metabolic Alkalosis and Chronic Furosemide Treatment on Serum Potassium (K^+) and Sodium (Na^+) Concentrations, Arterial P_{CO_2} and pH in the Dog

	Serum K^+ concentration (mEq/L)	Arterial P_{CO_2} (torr)	Arterial pH†	Serum Na^+ concentration (mEq)
Control	4.16 ± 0.31	36.1 ± 3.1	7.35 ± .04	148.1 ± 5.3
Acute respiratory alkalosis	3.33 ± 0.18*	22.0 ± 1.5*	7.54 ± .07*	146.9 ± 3.2
Acute metabolic alkalosis	3.25 ± 0.27*	37.5 ± 2.5	7.56 ± .05*	156 ± 9.4
Chronic furosemide treatment	3.27 ± 0.14*	34.9 ± 1.5	7.35 ± .05	144.7 ± 4.7

*$p<0.05$, Student's paired t-test when compared with control values

†Mean pH values were determined from individual hydrogen ion concentrations (nM/L)

TABLE 2
Muscle Sodium and Potassium Concentrations in Control (N = 10) and Furosemide-Treated Dogs (N = 12)*

	Na (mEq/kg)	K (mEq/kg)
Control	41.6 ± 3.0	80.9 ± 5.6
Furosemide treated	37.9 ± 4.3	58.7 ± 4.1†

*Mean ± SD

†$p<0.05$, Student's unpaired t-test when compared with control values

of sodium bicarbonate also produced significant elevation of arterial pH and reduction of serum potassium while not significantly altering arterial P_{CO_2} or serum sodium concentration (table 1). Daily furosemide treatment caused a steady reduction in serum potassium concentration. On the day of study, following 14 ± 4 days of treatment, all dogs demonstrated significant ($p<0.05$) reductions in serum potassium (table 1), while no significant changes were observed in serum sodium concentration. Four animals pretreated with furosemide were hyperventilated to arterial P_{CO_2} levels of approximately 20 torr without further reduction of serum potassium beyond that produced by furosemide itself (3.27 ± 0.14 mEq/L, table 1). Muscle potassium content was significantly ($p<0.05$) lower in dogs treated with furosemide than in untreated control animals (table 2).

Dogs receiving succinylcholine showed no alteration of the measured neuromuscular blockade parameters during acute respiratory alkalosis. Acute metabolic alkalosis significantly reduced latency period following 0.1 mg/kg succinylcholine (table 3). Furosemide pretreatment had no significant effect on succinylcholine-induced neuromuscular blockade when compared to control values (table 3).

Acute respiratory alkalosis reduced the time required to return to 90% control twitch tension following d-tubocurarine, while metabolic alkalosis had no consistent effects. Latency was significantly prolonged by acute metabolic alkalosis only, while maximum block obtained was unaltered. Chronic furosemide pretreatment had no effect on d-tubocurarine-induced neuromuscular blockade (table 4).

Acute respiratory and acute metabolic alkalosis decreased the time required to return to 90% of control twitch tension following pancuronium while furosemide pretreatment had no effect on rate of recovery. Neither acute respiratory and metabolic alkalosis nor chronic reduction of skeletal muscle potassium altered the latency period or maximum block obtained during pancuronium-induced neuromuscular blockade (table 5).

DISCUSSION

The present findings of a decrease in duration of pancuronium and curare neuromuscular blockade associated with acute respiratory and metabolic alkalosis are in agreement with previously published data.[1-5] It is generally believed that serum alkalosis enhances ionization of the 2 phenolic hydroxyl groups of d-tubocurarine, leading to a reduction in drug-receptor interaction. It is well known that acute extracellular alkalosis can lead to hypokalemia because of potassium entry into intracellular compartments.[6,8] This is further substantiated by our findings of significant decreases in serum potassium during both respiratory and metabolic alkalosis. Recently, Edwards et al found a 0.5 mEq/L decrease in serum potassium per 10 torr decrease in arterial CO_2 tension in surgical patients.[9] Their findings are compatible with our data in dogs.

Increased intracellular potassium $[K^+]_i$ along with a reduction of extracellular potassium $[K^+]_o$ should increase resting membrane potential,* thereby theoretically potentiating nondepolarizing and antagonizing depolarizing neuromuscular blocking agents. This is not substantiated by these results. The changes of $[K^+]_i$ to $[K^+]_o$ may be only theoretical within the pH ranges observed in this study since previous workers have

*$E = \frac{RT}{F} \log_e \frac{[K^+]_o}{[K^+]_i}$

where E = transmembrane potential
R = gas constant
T = absolute temperature
F = 1 faraday

TABLE 3

Effects of Succinylcholine During Control (C), Respiratory Alkalosis (RA), Metabolic Alkalosis (MA), and Chronic Furosemide Treatment (CFT) on Latency, Maximal Blockade Obtained, and Time to Return to 90% Control Twitch Tension*

Dose	Latency (sec)				Maximum block obtdined (%)				Time to return to 90% control (min)			
	C	RA	MA	CFT	C	RA	MA	CFT	C	RA	MA	CFT
0.03 mg/kg	23 ± 8	22 ± 11.3	18 ± 4.9	18.8 ± 4.8	96 ± 8	96 ± 3	98 ± 4	96 ± 5	14.8 ± 8.9	15.7 ± 7.1	15.8 ± 6.9	15.7 ± 5.9
0.1 mg/kg	12 ± 2	11.5 ± 4.4	7.8 ± 1.7†	10.2 ± 3.7	100 ± 0	100 ± 0	100 ± 0	100 ± 0	25.2 ± 8.6	26.3 ± 8.9	25.8 ± 5.9	25.6 ± 5.8

*Mean ± SD, $N = 4$

†$p<0.025$, Student's paired t-test when compared with control values

TABLE 4

Effects of d-Tubocurarine During Control (C), Respiratory Alkalosis (RA), Metabolic Alkalosis (MA), and Chronic Furosemide Treatment (CFT) on Latency, Maximal Blockade Obtained, and Time to Return to 90% Control Twitch Tension*

Dose	Latency (sec)				Maximum block obtained (%)					Time to return to 90% control (min)		
	C	RA	MA	CFT	C	RA	MA	CFT	C	RA	MA	CFT
0.1 mg/kg	78 ± 15.1	93 ± 11.5	91 ± 13.3	84 ± 11.7	41 ± 15.6	52 ± 11.0	46 ± 7.9	44 ± 11.1	12.2 ± 6.6	8.1 ± 3.3†	10.3 ± 4.9	13.3 ± 6.1
0.15 mg/kg	41 ± 12.6	53 ± 9.8	66 ± 12.1†	52 ± 10.8	89 ± 13.8	88 ± 9.1	91 ± 7.9	87 ± 12.2	23 ± 13.1	16.6 ± 7.9†	19.9 ± 12.2	25.2 ± 11.7

*Mean ± SD, $N = 4$

†$p<0.05$, Student's paired t-test when compared with control values

TABLE 5

Effects of Pancuronium Bromide During Control (C), Respiratory Alkalosis (RA), Metabolic Alkalosis (MA), and Chronic Furosemide Treatment (CFT) on Latency, Maximal Blockade Obtained, and Time to Return to 90% Control Twitch Tension*

Dose	Latency (sec)				Maximum block obtained (%)				Time to return to 90% control (min)			
	C	RA	MA	CFT	C	RA	MA	CFT	C	RA	MA	CFT
0.01 mg/kg	98 ± 12.3	116 ± 10.1	93 ± 12.9	102 ± 16.1	51 ± 12.9	60 ± 6.9	52 ± 11	66 ± 9.8	15.5 ± 3.2	9.6 ± 3.1†	8.9 ± 4.2	16.1 ± 4.1
0.015 mg/kg	62 ± 9.9	73 ± 9.3	68 ± 13.3	57 ± 10.8	86 ± 8.1	89 ± 12.0	89 ± 16.0	92 ± 6.8	26 ± 5.1	16.0 ± 3.2†	15.6 ± 4.1†	24.9 ± 6.7

*Mean ± SD, $N = 4$

†$p<0.05$, Student's paired t-test when compared with control values

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demonstrated no change in transmembrane potentials within these pH ranges.[10]

Our data show that furosemide pretreatment reduced both intracellular and extracellular $[K^+]$ by about 25%, ie 80.9 ± 5.6 to 58.7 ± 4.1 mEq/L (table 2) and 4.16 ± 0.31 to 3.27 ± 0.14 mEq/L (table 1), respectively. Therefore, the resting membrane potential should not change following equal proportional reduction of $[K^+]_i$ and $[K^+]_o$. Furosemide treatment did not significantly change extracellular (arterial) pH values in this study. These results would be compatible with the lack of observed effect from chronic furosemide treatment and subsequent total body potassium depletion on neuromuscular blocking agent action.

Four furosemide pretreated animals were hyperventilated to arterial Pco_2 levels of approximately 20 torr with subsequent serum alkalemia. However, no further reduction of serum potassium (mean = 3.2 mEq/L) was induced by the respiratory alkalosis. The neuromuscular blocking actions of d-tubocurarine and pancuronium were not affected by the addition of respiratory alkalosis in these animals. These results suggest that respiratory alkalosis without subsequent serum $[K^+]$ changes does not influence a nondepolarizing neuromuscular blockade and that the serum vs intracellular $[K^+]$ ratio may be important in determining the response to neuromuscular blocking agents. No good explanation can be offered for the lack of further hypokalemic effect of respiratory alkalosis in hypokalemic-furosemide-pretreated animals. It is possible that the electrochemical gradient across the cell membrane of potassium-depleted animals does not favor further exchange of K^+ for H^+ from the cell, since intracellular $[K^+]$ is already reduced. We have evidence to suggest that hypokalemia to below 3.0 mEq/L is difficult to achieve by serum alkalemia even when serum pH exceeds 7.7 (reference 8 and unpublished data), but hypokalemia to below 3.0 mEq/L can be induced by drug therapy or disease.

These data demonstrate that during chronic total body potassium depletion induced by furosemide, succinylcholine, d-tubocurarine, or pancuronium neuromuscular blockades are not altered. Thus, those patients who are chronically potassium depleted secondary to diuretic therapy should not demonstrate alteration in the response to neuromuscular blocking agent administration. These data further suggest that $[K^+]_i$ to $[K^+]_o$ ratio may influence neuromuscular blocking agent activity.

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Increased Sensitivity to Succinylcholine in a Patient Heterozygous for the Silent and the Fluoride-Resistant Gene

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Increased sensitivity to succinylcholine may be due to inherited variants of serum cholinesterase (acylcholine-acylhydrolase, E.C.3.1.1.8). Four different allelic genes at locus E_1 controlling human serum cholinesterase have been identified: the normal gene E_1^u, the atypical gene E_1^a, the fluoride-resistant gene E_1^f, and the silent gene E_1^s. These 4 genes give rise to 10 possible genotype combinations. The sensitivity of some of these genotypes to succinylcholine, as, for instance, homozygotes for the atypical enzyme E_1^a E_1^a, is well documented. However, the relation between some of the rarer genotypes and the sensitivity to succinylcholine is less well clarified.[1,2]

The present report represents the 1st case in which a peripheral nerve stimulator has been used to substantiate the increased succinylcholine sensitivity of a patient heterozygous for the silent and the fluoride-resistant gene, and the 2nd published case of prolonged apnea following succinylcholine in a patient carrying the E_1^f E_1^s genotype for abnormal serum cholinesterase.

Key Words—ENZYMES, cholinesterase. GENETIC FACTORS, cholinesterase. NEUROMUSCULAR RELAXANTS, succinylcholine.

A 51-YEAR-OLD otherwise healthy woman weighing 42 kg was admitted to the hospital for operation on an esophageal hernia. There was no history of any anesthetic complication in the family and she was currently receiving no medication. On the day of operation the patient was premedicated with meperidine 50 mg and atropine 0.4 mg IM. Following inhalation induction with N_2O, O_2, halothane, and succinylcholine 50 mg, to facilitate endotracheal intubation, anesthesia was maintained with N_2O and O_2 2:2 1, and halothane 0.5 to 1.5 percent. Following succinylcholine, the patient was apneic and obviously totally paralyzed for 30 minutes. After that time shallow respiratory movements were seen and over the next few minutes they gradually increased in force. Forty minutes after the injection of succinylcholine, gallamine 100 mg was given and the operation proceeded without difficulty. Recovery was uneventful.

Following this episode, the patient was referred to the Danish Cholinesterase Research Unit (DCRU)[3] for cholinesterase studies.

Three years later the patient was again admitted, this time for hysterectomy for a nonmalignant uterine tumor. As a consequence of a warning card issued by the DCRU, this center was contacted and, after an informed consent had been obtained, anesthetic management was planned which would permit quantitation of her response to succinylcholine. This included an indwelling radial artery catheter for measuring blood gases (and electrolytes) and the use of a peripheral nerve stimulator; the ulnar nerve was stimulated electrically at the wrist from a Disa stimulator (Ministim, type 14 E 01) by means of surface electrodes. The resultant force of adduction of the thumb was measured by a force-dis-

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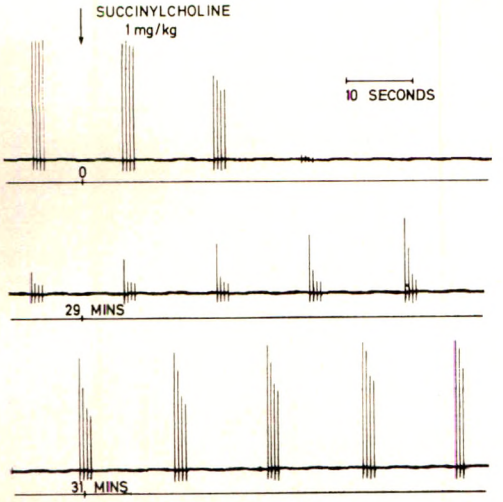


FIG 1. Dual block after an average clinical dose of succinylcholine (1.0 mg/kg) in a patient heterozygous for the fluoride-resistant and the silent gene ($E\ E_1^s$); train-of-four nerve stimulation. Train-of-four ratio: the ratio of the height of the 4th to the 1st resulting twitch. See text for further details.

placement transducer (Statham UC3 gold cell) surmounted by a UL4-10 load-cell accessory (preload, 200 g) and recorded on an Elema Mingograph 34®. A series of 4 supramaximal single shocks (rectangular pulse of 0.2 msec duration) was applied to the nerve at 2 Hz for 2 seconds every 12th second (train-of-four), as described by Ali et al.[4] Anesthesia was induced with thiopental 250 mg and maintained with N_2O, O_2, and halothane. Following succinylcholine (1 mg/kg) IV, the patient was apneic for 27 minutes. On return of spontaneous respiration, the response to train-of-four nerve stimulation showed a dual block (fig 1), which was even more pronounced following a further dose of succinylcholine given 45 minutes after the 1st dose (table 1).

Thirty-five minutes after the first injection of succinylcholine, respiration was clinically judged to be adequate, with a tidal volume of 490 ml.

METHODS

Serum cholinesterase activity was measured according to the procedure of Kalow and Lindsay.[5] Genetic variations of serum cholinesterase were identified by the following methods: dibucaine number,[6] fluoride number,[7] chloride number,[8] scoline number,[9] and urea number.[10,11]

The biochemical characteristics of serum cholinesterase variants at locus E_1 found by the DCRU[3] are given in table 2.

TABLE 1

Response to Train of Four Nerve Stimulation Following Injection of Succinylcholine in Patient Heterozygous for Fluoride-Resistant and Silent Gene ($E_1^f E_1^s$)

	Control twitch height, %	Minutes to: Spontaneous respiration	First evoked response to nerve stimulation	50% twitch height	90% twitch height	100% twitch height	Maximal twitch height (110%)
First injection of succinylcholine 1 mg/kg	100 (1.00)	27	25	29 (0.23)	30 (0.43)	31 (0.71)	45 (0.89)
Second injection of succinylcholine 1 mg/kg	110 (1.00)	30	24	28 (0.00)	30 (0.00)	31 (0.00)	46 (0.50)

Numbers in brackets indicate train-of-four values; that is, the ratio of the height of the 4th to the 1st resultant twitch in the train. Note dual block after the 1st injection of succinylcholine (low train-of-four values). Note also the even more pronounced dual block after the 2nd injection of succinylcholine, given 45 minutes after the 1st injection.

TABLE 2
Biochemical Characteristics of Serum Cholinesterase Variants at the E_1 Locus [3]

Genotype	No. of patients	Cholinesterase activity, u/L	Dibucaine No.	Fluoride No.	Chloride No.	Scoline No.	Urea No.
$E_1^u\ E_1^u$*	453	677-1560	78-86	55-65	1-22	89-95	41-52
$E_1^u\ E_1^a$*	338	474-1110	53-72	40-54	13-34	56-77	53-70
$E_1^a\ E_1^a$*	104	166-757	13-27	15-30	41-59	4-25	84-100
$E_1^u\ E_1^s$*	33	385-870	78-85	56-64	7-17	86-93	42-53
$E_1^a\ E_1^s$*	19	96-489	12-30	20-35	43-60	4-28	87-100
$E_1^s\ E_1^s$	3	0	. . .	. . .	. . .	. . .	. . .
$E_1^u\ E_1^f$†	13	611-1150	74-79	46-51	16-30	84-91	63-68
$E_1^a\ E_1^f$†	5	475-648	48-52	25-33	30-42	54-60	84-95
$E_1^f\ E_1^s$†	2	351-509	63-64	26-38	25-26	80-81	90-91

*Indicates that 2½ and 97½ percentiles are given
†Indicates that ranges are given

The nomenclature of Motulsky[12] is used.

RESULTS

Serum cholinesterase activity was 351 μL, dibucaine number (DN) 63, fluoride number (FN) 26, chloride number (ClN) 25, scoline number (Scn) 81, and urea number (UN) 91. The patient was therefore classified as $E_1^f\ E_1^f$ or $E_1^f\ E_1^s$ (compare table 2).

To decide which of the 2 genotypes ($E_1^f\ E_1^f$ or $E_1^f\ E_1^s$ was present, a family study was done and, as can be seen from tables 2 and 3 and fig 2, this resulted in the final classification of the patient as $E_1^f\ E_1^s$.

DISCUSSION

It is impossible to differentiate between the various genotypes using serum cholinesterase activity alone (table 2). Differential inhibition technics with, for instance, dibucaine, fluoride, chloride, succinylcholine (scoline), and/or urea must also be used. Using dibucaine (in a 10^{-5} molar concentration) as an inhibitor, cholinesterase activity in serum from individuals homozygous for the usual enzyme ($E_1^u\ E_1^u$), heterozygous for the usual and the atypical enzyme ($E_1^u\ E_1^a$), and homozygous for the atypical enzyme ($E_1^a\ E_1^a$) will be inhibited 78 to 86 percent, 53 to 72 percent and 13 to 27 percent, respectively (table 2). Thus, differentiation of these most common genotypes can be made using dibucaine alone. When the rarer genes (E_1^s and E_1^f) are concerned, it appears that the dibucaine number (DN) as well as the cholinesterase activity overlap—for instance, $E_1^u\ E_1^a$ and $E_1^f\ E_1^s$. No single inhibitor can distinguish all genotypes of locus E_1. The genotypes can, however, be separated, if the results of inhibition with 2 or more inhibitors are compared (table 2).

As judged from DN and ClN, our patient could be either heterozygous for the usual and the atypical gene ($E_1^u\ E_1^a$), heterozygous for the fluoride-resistant and silent gene ($E_1^f\ E_1^s$), or homozygous for the fluoride-resistant gene ($E_1^f\ E_1^f$). (This latter genotype is not listed in table 2, since we have had no such patient referred to the DCRU. Inhibitor numbers are, however, the same for $E_1^f\ E_1^s$ and $E_1^f\ E_1^f$, since the gene E_1^s is "silent"). Comparing further the patient's FN, ScN, and UN with table 2, it appears, however, that she could not be $E_1^u\ E_1^a$. We are then left with 2 possibilities, the patient being either $E_1^f\ E_1^f$ or $E_1^f\ E_1^s$. These 2 genotypes can only be distinguished with certainty by family studies (as the inhibitor numbers are the same).

Table 3 and fig 2 show that the patient's children were $E_1^u\ E_1^s$ and $E_1^a\ E_1^f$. This finding still left doubt whether the patient was $E_1^f\ E_1^f$ or $E_1^f\ E_1^s$. However, investigation of the patient's brothers and sisters (generation II, patients No. 1, 2, 3, 5, 6, and 7) disclosed that 3 different genes were represented—namely, E_1^u, E_1^s, and E_1^f—and that 2 persons (patients No. 2 and 3) were $E_1^u\ E_1^u$. Therefore, both parents (generation I, patients No. 1 and 2) had to have an E_1^u gene, one parent being $E_1^s\ E_1^s$ and the other $E_1^u\ E_1^f$. Thus, the patient could not

TABLE 3

Biochemical Characteristics and Presumed Genotypes of the Family*

Generation	Patient No.	Cholinesterase activity, u/L	Dibucaine No.	Fluoride No.	Chloride No.	Saline No.	Urea No.	Presumed genotype		Age, years
II	1	509	64	38	26	80	90	$E_1^f E_1^s$		53
	2	775	82	62	13	91	50	$E_1^u E_1^u$ / $E_1^u E_1^s$	or	60
	3	1211	83	62	19	94	52	$E_1^u E_1^u$		57
	4	762	66	44	25	59	67	$E_1^u E_1^a$		52
	5	393	82	63	9	100	46	$E_1^u E_1^s$		48
	6	823	74	46	19	88	64	$E_1^f E_1^u$		63
	7	906	76	47	16	86	64	$E_1^f E_1^u$		46
	8†	351	63	26	25	81	91	$E_1^f E_1^s$		51
	9	1115	67	43	26	71	63	$E_1^a E_1^u$		55
III	1	675	79	61	16	90	48	$E_1^u E_1^s$		26
	2	385	82	56	7	85	48	$E_1^u E_1^s$		28
	3	865	84	62	10	90	48	$E_1^u E_1^u$ / $E_1^u E_1^s$	or	18
	4	1484	83	59	13	91	47	$E_1^u E_1^u$		32
	5	805	82	60	21	91	50	$E_1^u E_1^u$		35
	6	158	12	29	60	4	100	$E_1^a E_1^s$		21
	7	762	74	47	30	91	67	$E_1^f E_1^u$		28
	8	648	48	27	32	60	84	$E_1^a E_1^f$		25
IV	1	1238	82	60	13	90	45	$E_1^u E_1^u$		½
	2	1000	83	57	13	95	44	$E_1^u E_1^u$		4
	3	1138	85	59	16	91	49	$E_1^u E_1^u$		6
	4	996	82	57	18	91	48	$E_1^u E_1^u$		11

*Nomenclature of Motulsky[12]

†Propositus

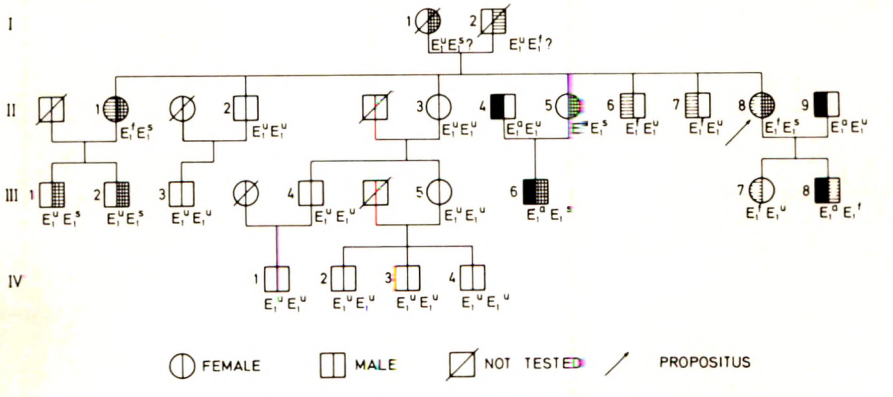


FIG 2. Genotype relationship of the family

be E_1^f E_1^f, but had to be E_1^f E_1^s. This genotyping is further supported by the finding that the children (generation III, patients No. 1 and 2) of one sister with a presumed genotype of E_1^f E_1^s (generation II, patient No. 1) had low serum cholinesterase activity, and, therefore, probably were E_1^u E_1^s.

Of the abnormal genes, E_1^a is the most frequently found in Caucasians, but it is found relatively seldom in other ethnic groups.[13] The E_1^f and E_1^s genes are rare in most Caucasian populations.[14] In a recent investigation of 1278 persons in Denmark, we found that 97.2 percent were E_1^u E_1^u, 2.5 percent were E_1^u E_1^a, 0.24 percent were E_1^u E_1^f, and 0.08 percent (1 patient) was E_1^a E_1^a. We did not find any other phenotypes of cholinesterase.[15]

The genotype E_1^f E_1^s is extremely rare. Wittaker[16] was the first to identify a patient with this genotype. However, the patient was not given succinylcholine. Simpson[17] in 1967 was the first to report prolonged apnea (20 minutes) after succinylcholine (30 mg) in a patient with this genotype. Since then, only a few patients with genotype E_1^f E_1^s have been identified,[18,19] and only Lehmann and Liddell[2] have reported a case of prolonged apnea after succinylcholine. They did not, however, state the duration of apnea. In the present case, 27 minutes of apnea were induced. This is in good agreement with that reported by Simpson,[17] when the dose of succinylcholine is taken into account.

Succinylcholine was originally believed to produce a pure depolarizing block in man (fig 3). It has now been demonstrated, however, that prolonged or repeated administration of succinylcholine in a patient with normal serum cholinesterase produces an initial depolarizing block (phase I block), which relatively suddenly changes to a nondepolarizing block (phase II or dual block, fig 4.)[20-22] Recent evidence suggests that the prolonged apnea after an average clinical dose of succinylcholine (0.5 to 1.0 mg/kg) in patients homozygous for the atypical enzyme (E_1^a E_1^a) is also characterized by a dual block.[23,24] The present case indicates (fig 1 and table 1) that the same may happen in patients heterozygous for the fluoride-resistant and the silent gene (E_1^f E_1^s).

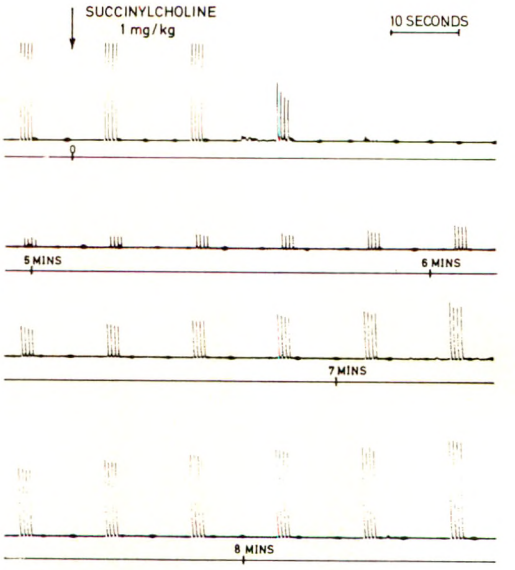


FIG 3. Typical depolarizing neuromuscular block after succinylcholine in a normal patient (E_1^u E_1^u) using train-of-four nerve stimulation. Note the equal height of all 4 resulting twitches of the thumb.

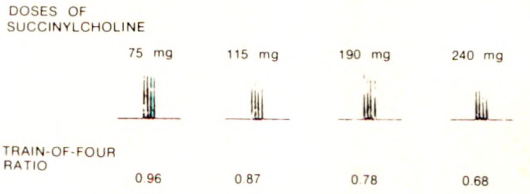


FIG 4. Dual block after repeated doses of succinylcholine in a normal patient (E_1^u E_1^u) using train-of-four nerve stimulation. Note the falling train-of-four ratio.

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DISCONTINUING ANTICOAGULANTS BEFORE SURGERY

The records of 159 patients with previous cardiac valve replacement who had subsequently undergone 180 noncardiac operations were reviewed. The operations were from less than 3 months to more than 10 years following valve replacement. All patients were receiving anticoagulants before the noncardiac operations. There were several patterns of anticoagulant discontinuance before surgery and reinstitution after surgery, as well as continuation throughout the surgical period. The overall incidence of documentable thromboembolic complications was approximately 10%. None of the postoperative complications occurred while the patient was in hospital, with the earliest such complication seen 2 years later. Patients receiving anticoagulants on a long-term basis did, however, have a 13% incidence of various difficulties with hemostasis during and following the noncardiac operations. The authors conclude that there is a minimal risk to patients with cardiac valve prostheses who are receiving anticoagulants when the drug regimen is stopped for 1 to 3 days preoperatively and 1 to 7 days postoperatively. *(Tinker JH, Tarhan S: Discontinuing anticoagulant therapy in surgical patients with cardiac valve prostheses. JAMA 239:738-739, 1978)*

Reverse Arterial Blood Flow as a Pathway for Central Nervous System Toxic Responses Following Injection of Local Anesthetics

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In baboons, lidocaine HCl was injected into the lingual (3 mg/kg), brachial (7 mg/kg), or femoral (7 mg/kg) arteries. Blood samples were taken from the internal carotid artery (ICA), internal jugular (IJV), external jugular (EJV), brachial (BV), or femoral (FV) vein, depending on the injection site, 6, 30, and 180 seconds after injection. Subsequently, radioactive microspheres (20 μ in diameter) were injected into the lingual artery, and the brains were obtained 48 hours later at postmortem to locate the microspheres.

Six seconds after injection into the lingual artery, lidocaine concentration in ICA was 28 μg/ml, whereas peak levels in IJV and EJV occurred at 30 seconds, being 51 and 25.7 μg/ml, respectively. After injection into the brachial artery, peak average ICA levels were 105.5 μg/ml at 6 seconds, while only 20.6 μg/ml concentration was noted in ICA after injection into the femoral artery.

Seventy-four percent of the Sr^{90} labeled microspheres were found lodged in the ipsilateral cerebral hemisphere.

Local anesthetic drugs accidentally injected into arteries may reach the cerebral circulation following a centripetal pathway and thus produce central nervous system toxic responses.

Key Words — TOXICITY, local anesthetics. ANESTHETICS, local, toxicity.

PREVIOUSLY, in a study of patients allegedly allergic to local anesthetic drugs, we established that true allergy was indeed very rare, and determined that most untoward reactions were due to maladministration, to drug interaction, or to psychogenic responses.[1] Among these allegedly allergic cases, there were several in which signs of toxicity developed, including convulsions and loss of consciousness, even when relatively small doses (1.8 ml of 2% lidocaine HCl) were injected in the area of the head and neck to obtain local anesthesia. Other authors have encountered similar cases, with ensuing mortality in some instances.[2-4]

The observations described here include studies conducted in baboons indicating the possibility that arterial blood flow, not only in the head but also in the extremities, may be reversed when retrograde injections are made intra-arterially. Depending on the rate of injection, dose, volume, and the arterial pressure of the recipient, the drugs administered may reach the cerebral circulation, resulting in neurotoxicity even though systemic venous blood levels may not be excessive.

METHODS

Female baboons, weighing between 12 and 16 kg, were tranquilized with ketamine HCl 5 mg/kg IM; thereafter thiopental sodium

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10 mg/kg was given IV and the trachea intubated. Mechanical ventilation was conducted with a Harvard pump respirator, with a tidal volume of 10 ml/kg, at a rate appropriate to maintain arterial P_{CO_2} around 34 torr. Pancuronium bromide 0.15 mg/kg was used to allow control of respiration. In all experiments, cannulation of one internal carotid artery (ICA), internal jugular (IJV) and external jugular (EJV) veins was done. In 8 instances, the ipsilateral lingual artery was dissected and a #23-g scalp vein needle inserted retrograde. None of the cannulated vessels was ligated distally. Lidocaine HCl 3 mg/kg (in a 2% solution) was rapidly injected into the lingual artery, and 8-ml samples of blood were taken from the ICA, IJV, and EJV, 6, 30, and 180 seconds after injection. Thereafter a second injection of 2 ml of saline solution containing radioactive microspheres, 20 μ in diameter, tagged with radioactive strontium (Sr^{90}), was made into the lingual artery in a similar fashion. Arterial blood pressure was monitored continuously by means of a strain gauge. End-tidal CO_2 tension was measured through a CO_2 infrared gas analyzer.

After a recovery period of 2 weeks, during which the animals received IM iron and antibiotics, a second experiment was made on the opposite side. After cannulating ICA and IJV, the ipsilateral brachial artery (BA) and vein (BV) were dissected in 4 experiments. The vein was cannulated, and in the artery a #23-g scalp vein needle was introduced retrograde. In 4 other animals the femoral vein (FV) was cannulated and the needle inserted into the femoral artery (FA). Lidocaine HCl 7 mg/kg was injected as a 2% solution in each case, into either the BA or the FA; blood samples from the ICA, EJV, and BV were obtained in the former, while in the latter the FV was also sampled, 6, 30, and 180 seconds following injection.

At the completion of this last experiment, the animals were sacrificed with an overdose of sodium thiopental. The brains, including meningeal covers, were obtained postmortem; after tissue sectioning, the location and concentration of the injected microspheres were determined quantitatively with a scintillation counter. Analysis of the blood samples for lidocaine HCl concentration was done using a Hewlett Packard 402 gas chromatograph having 2 columns packed with 3% OV-17 material.[5]

RESULTS

The average distribution of the Sr^{90} labeled microspheres injected into the lingual arteries was 74.2% to the ipsilateral cerebral hemisphere, and 10.5% in the opposite side of the brain. In the cerebellum and the meninges, 6.1% and 4.5% of the microspheres were found, respectively. Unaccounted for were 3.7%, which were most likely distributed centrifugally.

The mean and SD of lidocaine concentrations in blood after injection of 3 mg/kg into the lingual arteries are shown in fig 1.

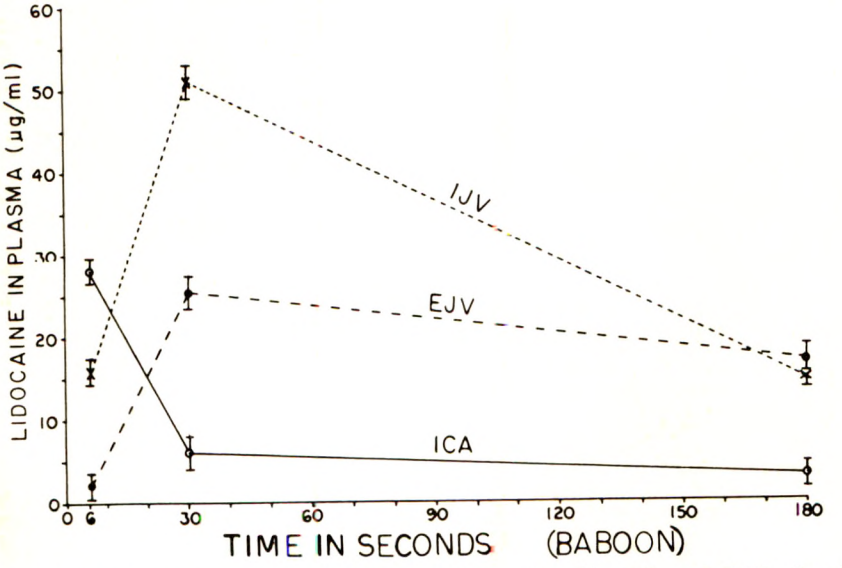


FIG 1. Average plasma concentrations of lidocaine HCl in the ICA, IJV, and EJV after injection of 3 mg/kg into the lingual artery

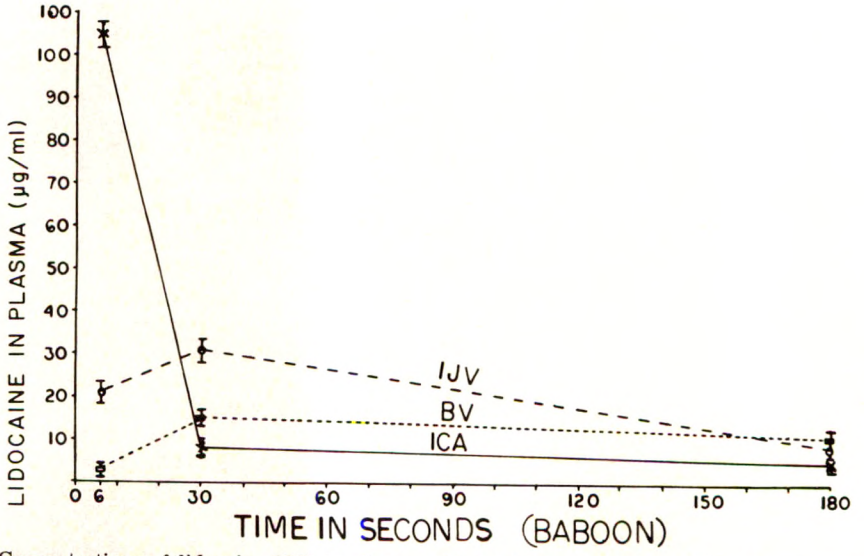


FIG 2. Concentrations of lidocaine HCl in plasma obtained from the ICA, IJV, and BV after the injection of 7 mg/kg into the brachial artery

Six seconds after injection, a mean level of 28 µg/ml was found in the ICA, whereas the peak mean levels in IJV and EJV occurred at 30 seconds, being 51 and 25.7 µg/ml respectively.

When 7 mg/kg of lidocaine were injected centripetally into the brachial artery, an average of 105.5 µg/ml was found in the ipsilateral ICA 6 seconds later; this level promptly fell, and by 30 seconds it was only 8.4 µg/ml. Concentrations in IJV and BV followed a parallel course, though at different levels, up to 180 seconds (fig 2).

Injection of the same amount into the femoral artery produced a mean blood level of 20.6 µg/ml in the ICA 6 seconds thereafter. Changes of concentration in the BV and EJV were again similar. In the femoral vein, however, a peak level of 66.7 µg/ml was found 30 seconds after injection (fig 3).

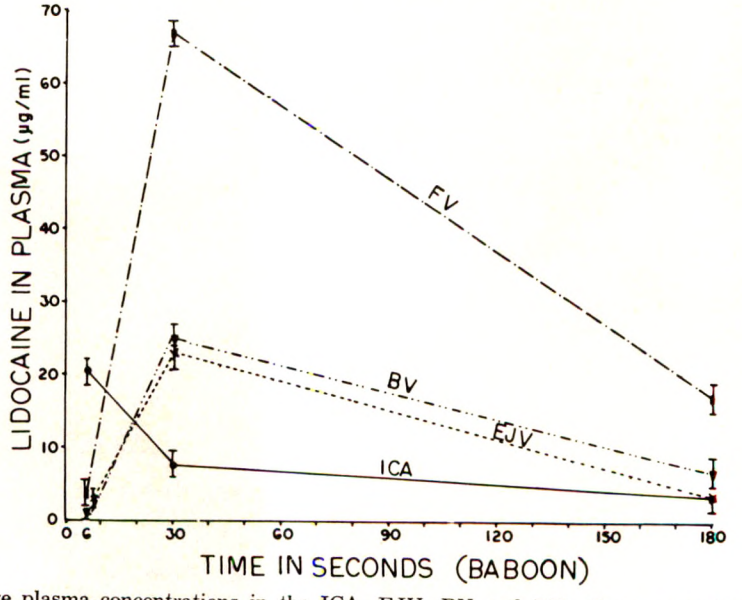


FIG 3. Average plasma concentrations in the ICA, EJV, BV and FV after centripetal injection of 7 mg/kg of lidocaine HCl into the femoral artery

DISCUSSION

Central nervous system toxicity resulting from administration of local anesthetic drugs to patients results from elevated blood concentration in the cerebral circulation. Depending on the vascularity of the tissue injected and the presence or absence of vasoconstrictors, local anesthetic agents will reach maximum blood concentrations from 5 to 30 minutes after injection. According to Bromage and Robson,[6] Mazze and Dunbar[7] with lidocaine HCl, and Tucker et al[8] with mepivacaine HCl, maximum blood levels resulting after epidural, caudal, intercostal, brachial plexus, IV regional, and femorosciatic blocks seldom exceed 6 to 8 μg/ml, with peak concentration occurring around 20 minutes post injection. This drug accumulation takes place as absorption from the injected site into the bloodstream occurs.

For toxicity to develop, it is usually required that an overdose of the anesthetic drug be administered and/or that the rich vasculature of the injected tissue is not taken into consideration.

A number of clinical cases have been reported in which signs of toxicity (ie, somnolence, loss of consciousness, tremor, analgesia, numbness of the lips, convulsions, respiratory and cardiac arrest) appeared soon after administration, and in some cases even during injection, of the anesthetic, suggesting direct intravascular entry.[9-13] If the drug is administered IV, doses approaching one-half to two-thirds of the recommended maximum safe dose are usually necessary to produce central nervous system toxicity.[14,15] Intraarterial injections have been assumed to follow the same pathway of distribution after centrifugally going through the capillary bed and then entering the venous vasculature.[16] The immediate occurrence of postinjection convulsions in some instances,[1,17,18] even more common in dental practice,[13,19,20] may, however, be evidence that the administered drug follows a centripetal flow, when injection is made at a pressure level that exceeds arterial pressure.

In a previously reported study using rhesus monkeys,[21] we have shown that injection of 3 mg/kg of lidocaine into the facial artery results in electroencephalographic changes 6 seconds after injection, even before cardiovascular effects are evident. Similarly, and through the same route, a cerebral angiogram can be obtained when 3 ml of contrast media are administered (fig 4).

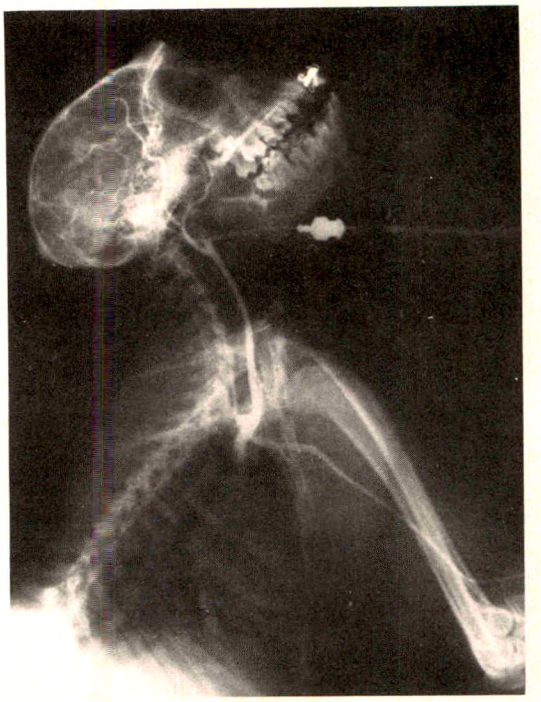


FIG 4. Cerebral angiogram depicting the internal and common carotid and even the axillary arteries of the rhesus monkey. Contrast medium was injected into the facial artery. (From J Am Dent Assoc 94: 1142, 1977. Copyright by the American Dental Association. Reprinted by permission.)

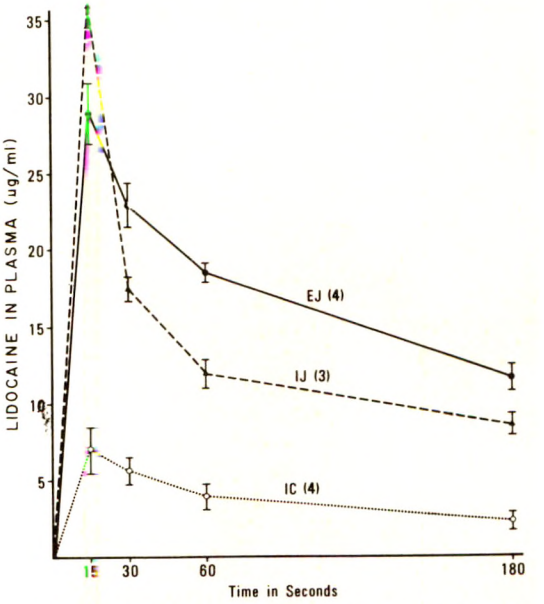


FIG 5. Mean blood concentrations of lidocaine HCl obtained from the internal carotid artery (IC), internal jugular (IJ), and external jugular (EJ) veins after injection of 3 mg/kg into the facial artery of a dog. (From Oral Surg 44:167, 1977. Reprinted by permission.)

In a subsequent study the injection of 3 mg/kg of lidocaine into the facial artery of dogs resulted in internal carotid artery blood levels between 5 and 7 μg/ml 15 seconds later. Internal and external jugular vein blood levels exceeded 30 μg/ml at the same time (fig 5). When the same amount of lidocaine was injected into the facial vein, carotid blood levels were less than 3 μg/ml, peaking at 30 seconds. Concentrations of the local anesthetics in the jugular vein peaked at 15 seconds, exceeding 35 μg/ml.[22] It is probable that because the first blood sample was obtained 15 seconds following injection, the actual peak concentration of the local anesthetic was missed.

These two preliminary observations provided data indicating that reversibility of arterial blood flow among some of the terminal branches of the carotid vascular bed was possible. However, the cerebral circulations of both rhesus monkeys and dogs differ from that of man. Moreover, although EEG changes in rhesus monkeys were noted at 6 seconds, samples for lidocaine determination were taken at 15 seconds in the canine study. The present observations made in baboons, which have a cerebral circulation more closely resembling man's, show that plasma lidocaine concentrations in the ICA 6 seconds following injection were higher than what are generally considered to be toxic blood levels in primates.[23]

Extrapolation of a study by Penn et al[24] with computerized axial tomography density measurements indicated the cerebral blood volume at any one time to be 3 ml/100 ml of brain tissue, equivalent to about 30 ml of blood in the whole adult human brain at any given moment. Thus although only small quantities of the anesthetic drugs are commonly injected about the head in the clinical situation, the entrance of even 1 mg (1000 μg) of lidocaine HCl into the internal carotid artery could indeed produce arterial blood levels of 20 μg/ml ± 2 μg/ml, at which levels toxic manifestations have been observed in rhesus monkeys[23] and man.[25]

The lodging of most of the radioactively labeled microspheres in the capillary beds of the brain and adjacent structures also indicates the presence of this phenomenon. Further observations remain to be made to elucidate whether greater concentrations in the ipsilateral ICA result in contralateral seizures. A simultaneous centrifugal distribution of local anesthetic was evident from the high blood concentrations, peaking 30 seconds after injection, noted in the brachial and femoral veins when injections of 7 mg/kg were made in their corresponding arteries.

Elevated concentrations of lidocaine in the ICA after injection into the brachial and femoral veins may explain other reported cases of immediate central nervous system toxicity[26-28] during distal injection of local anesthetic drugs. This observation is not surprising, since cerebral angiography has been performed by injection of contrast media into the brachial artery under pressure.[29] Also, Downs et al[30] have demonstrated that even when only 3 ml of contrast media are used to irrigate radial arterial cannulae, visualization of the subclavian and vertebral arteries is possible, thus establishing the possibility of reversed arterial flow traveling distances greater than 60 cm.

In conclusion, these prior observations, along with the present study, not only reaffirm the reversibility of carotid blood flow with parenteral administration of drugs in the area of the head and neck, but also indicate that under certain circumstances this same complication may occur when injections are made in more distal areas such as the arm and groin. Repeated aspiration and the design of needles and syringes that would more easily allow intravascular lumen identification are recommended to prevent inadvertent intra-arterial injections.

ACKNOWLEDGMENTS

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DELAYED HEMOLYTIC TRANSFUSION REACTIONS

Delayed hemolytic transfusion reactions in 8 patients were manifested solely or primarily by an apparently unexplained posttransfusion decrease in the hematocrit value. Alloantibodies were eventually found in all 8 patients, but were sometimes undetectable for as long as 72 hours after the reaction. Absence of the alloantibodies did not preclude the occurrence of a new, acute hemolytic reaction. There were 3 instances of reversible renal failure complicating the reaction. In 2 patients, some or all of the antibodies became undetectable after 4 and 9 months. Patients previously sensitized to RBC antigens should have available records inspected and a warning device (wristband or wallet card) provided to help prevent reactions caused by an anamnestic antibody response. *(Solanki D, McCurdy PR: Delayed hemolytic transfusion reactions: an often-missed entity. JAMA 239:729-731, 1978)*

Effect of Subanesthetic Concentrations of Enflurane and Halothane on Human Behavior

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Ten male volunteers performed 3 tasks before, during, and following administration of 3 levels of alveolar halothane (0.05, 0.1, and 0.2%) for one-half hour each and (on a separate occasion) enflurane (0.15, 0.3, and 0.4%) for one-half hour each. The concentrations of halothane tested represented 7, 13, and 27% of MAC values, respectively; those of enflurane were 9, 18, and 24% of MAC. The tasks were a choice-reaction time test, a digit span test, and a Purdue Pegboard Assembly test. Volunteers also were tested for amnesia with word pairs and a picture. No effects or only slight effects on mental function could be detected at the lowest concentrations of either agent. At higher concentrations both agents impaired function, as indicated by an increase in reaction time, decreased ability to remember numbers, and decreased ability to assemble a simple structural array. Amnesia for word pairs but not pictures occurred at 27% of MAC for halothane and 18% of MAC for enflurane. All test scores reverted to control levels within one-half hour after discontinuing the anesthetic. Our results indicate that subanesthetic but not trace levels of enflurane or halothane can impair mental performance and manual dexterity and produce amnesia. The levels of anesthetic required far exceed those experienced by operating room personnel. However, such levels might be found for several hours in patients following prolonged anesthesia.

Key Words—ANESTHETICS, volatile, halothane. ANESTHETICS, volatile, enflurane. ANESTHETICS, volatile, trace concentrations. PSYCHOLOGIC RESPONSES.

THE impact of trace concentrations of inhaled anesthetic gases and vapors on human behavior remains in question despite its potential importance both to operating personnel[1] and to patients recovering from anesthesia. Bruce et al reported that 0.001% halothane combined with 0.05% N_2O significantly impaired mental performance in volunteers.[2,3] Bruce and Bach subsequently found significant mental impairment with 0.005% N_2O alone but no measurable decrements in performance in subjects exposed to 0.0025% N_2O plus 0.00005% halothane.[4] However, Garfield et al[5] and Smith and Shirley[6] could not document mental impairment in volunteers at substantially higher anesthetic concentrations. Garfield et al demonstrated impairment with 20 and 30% but not 5 or 10% N_2O. Smith and Shirley found no impairment in anesthetists ex-

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posed to 0.01% halothane for 3 to 4 hours. Similarly, we found no effects from 0.1, 0.2, or 0.4% N_2O or from 0.001 or 0.01% halothane (alveolar concentrations). Twenty and 30% (but not 10 or 5%) N_2O or 0.1% halothane produced significant impairment.[7] The present investigation sought to determine whether equivalent doses of enflurane were required to produce mental impairment. We also explored the dose-response relationship between enflurane or halothane and mental function. Our test systems were patterned after the most sensitive tests used by Bruce and his coworkers.[2-4] Our results suggest that enflurane and halothane influence behavior at subanesthetic levels (eg, 0.1 to 0.2% alveolar halothane or 0.3 to 0.4% alveolar enflurane), but, as with N_2O, these levels far exceed those found in the operating suite. For example, in unscavenged air from operating rooms, the halothane concentration may range from 0 to 0.005% with an average value of 0.001%.[1]

METHODS

Ten normal, 21- to 25-year-old male college students volunteered for this study. Each subject was in good general health without a current history of prescription or nonprescription drug ingestion. The study was explained to the subjects and informed consent obtained. Chest x-ray, complete blood count, and liver enzyme profile were within normal limits. Volunteers avoided strenuous physical exertion, late-night activities, and stimulants such as coffee or tea for at least 12 hours before testing. There were 3 test sessions, each session separated from the next by intervals of 1 week. Testing was done in a quiet, isolated room on a Datapoint computer terminal programed to administer and record data from a digit span test and a choice reaction time test. Tests of manual dexterity (Purdue Pegboard) and amnesia also were given.

The digit span test requires that the subject remember and reproduce a series of random digits presented sequentially at a rate of one per second, for 200 milliseconds, by the computer on a cathode ray tube. Initially, 4 digits appear. After presentation of the final digit, the volunteer types the whole number into the computer. He is tested at the same level twice, eg, two 4-digit numbers. If at least 1 response is correct, the test is repeated at the 5-digit level. The number of digits is successively increased until the volunteer fails to reproduce either number correctly at a given level. The test then begins again starting with a 4-digit number, but the volunteer now must recall the numbers in reverse order. Again, the test ends when he misses both numbers at the same level. The results are stored on cassette tape for future analysis. The total score is the sum of the longest forward and backward string correctly reproduced; eg, 9 forward and 8 backward would be scored as 17. In our subjects, the control score usually ranged from 14 to 20.

The choice reaction test is a divided-attention audiovisual task. A zigzag or straight-line display of dots (12 per second) appears on the Datapoint cathode ray tube. A simultaneous auditory stimulus of fast (180 per minute) or slow (90 per minute) clicks emanates from earphones. Every 3 to 8 seconds the auditory and/or the visual displays change randomly to 1 of the 3 other possible combinations. The possible combinations are straight line–fast clicking, straight line–slow clicking, zigzag line–fast clicking, or zigzag line–slow clicking. The subject must determine when a change occurs, identify the new combination, and press a key indicating the identity of the new combination. The time required to press the key and the accuracy of the answer are recorded separately on magnetic tape. Normal response times are 1.0 to 1.5 seconds. Each test sequence contains 50 choice responses which subsequently are transmitted to the campus 360 IBM computer for calculation of the mean reaction time, SD, and number of correct responses.

The Purdue Pegboard test was administered after the choice reaction test.[8] In this test the subject has 60 seconds to assemble pins, collars, and washers in a fixed repetitive array. The total number of parts assembled is the score. With practice, the average score equaled 40 to 50 pieces.

The first session was exclusively devoted to control measurements. The anesthetic exposures began only after orientation and control data yielded consistent test scores (ie, a plateau in test scores was obtained indicating no further effect of learning). The second and third sessions began and ended with a control session. The sessions for a given subject were conducted at the same time of day. Volunteers were unaware of which anesthetic they were inhaling and of the sequence in which the various concentrations were administered. Gases were administered through a Lloyd nonrebreathing

TABLE 1
Halothane and Enflurane Doses and Sequence

	Halothane			Enflurane		
	Inspired concentration (%)	Alveolar concentration (%)	Fraction of 1 MAC	Inspired concentration (%)	Alveolar concentration	Fraction of 1 MAC
Control	0	0	0	0	0	0
Anesthetic exposures	0.1	0.05	0.07	0.2	0.15	0.09
	0.2	0.1	0.13	0.42	0.3	0.18
	0.4	0.2	0.27	0.53	0.4	0.24
Control	0	<0.05	<0.07	0	<0.02	<0.02

valve* via a mouthpiece. A nose clamp prevented inhalation of room air. A Rahn sampler obtained a continuous end-tidal sample, which was analyzed with a Perkin Elmer 1100 mass spectrometer. The result was recorded on a Gilson pen polygraph. The mass spectrometer was calibrated with test-gas standards at half-hour intervals.

Each subject was tested at 3 alveolar concentrations of halothane (0.05, 0.1, and 0.2%) and, on a separate occasion, 3 alveolar concentrations of enflurane (0.15, 0.3, and 0.4%). The anesthetic dose that these 3 alveolar concentrations represent are roughly equivalent in terms of MAC (table 1). Anesthetic concentrations were administered in order of increasing magnitude. Volunteers were instructed to discontinue breathing any mixture if they experienced dyspnea or syncope.

Each session began with the subject breathing room air through the rebreathing system and taking the digit span, choice reaction time, and Purdue Pegboard tests to establish control values. Then anesthetic administration was begun with the agent being delivered at an inspired concentration sufficient to maintain the alveolar concentrations indicated in table 1 for half-hour periods.

After breathing each concentration for 10 minutes, one of six 8 by 10 inch pictures, one of six word pairs, and one-inch letters on an 8 by 10 inch cardboard background were sequentially presented to the volunteer for 30 seconds. The word pair was spoken by the examiner and repeated by the volunteer. The volunteer was instructed to remember both the picture and word pair. While still breathing the anesthetic, the subject took the digit span, choice reaction time, and Purdue Pegboard Assembly tests. Anesthetic administration then was discontinued and the subject was allowed several minutes to recall the picture and exact word pair.

The same sequence of anesthetic administration and testing was carried out for the remaining two anesthetic concentrations, followed by a final control testing with room air.

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STATISTICS

Control value means were compared with experimental value means using a paired *t*-test. We accepted as significant a *p* value of less than 0.05. A chi-square analysis was performed to determine the statistical significance of possible development of amnesia.

RESULTS

The 0.07 and 0.13 MAC halothane did not affect digit span scores, but the 0.27 MAC halothane decreased the digit span score to 10.4 (a 39% decrease from control) (table 2, fig 1). With this and all other tests for either halothane or enflurane, the post-exposure control did not differ from the preexposure control. Breathing 0.07, 0.13, and 0.27 MAC halothane significantly increased choice reaction time (table 2, fig 2). The 0.13 and 0.27 but not the 0.07 MAC halothane significantly decreased correct responses. All halothane exposures significantly decreased the Purdue Pegboard Assembly scores. No amnesia for word pairs or pictures was seen during control testing (table 3). A dose-related appearance of amnesia occurred with a greater sensitivity for word-pair testing (table 3).

At concentrations exceeding 0.09 MAC enflurane, the digit span total score decreased significantly in a dose-related fash-

TABLE 2

Relationship of Anesthetic Dose to Altered Mental Function

Exposure	N	Digit span total, mean ± SE	Choice reaction (sec), mean ± SE	Choice responses (% correct), mean ± SE	Purdue Pegboard (assembly for 60 sec), mean ± SE	Change from control (%)		
						Digit span	Choice reaction	Purdue Pegboard
Halothane								
Control	10	18.2 ± .9	1.18 ± .09	95.7 ± 1.3	48.0 ± .9	0	0	0
0.07 MAC	10	18.8 ± .8	1.30 ± .11*	92.1 ± 2.4	45.4 ± 1.2*	3.7 ± 2.5	9.6 ± 2.3	−5.3 ± 2.4
0.13 MAC	10	17.0 ± .7	1.61 ± .15*	81.3 ± 5.5*	38.9 ± 1.9*	−5.9 ± 3.6	40.2 ± 9.0	−18.5 ± 4.7
0.27 MAC	8	10.4 ± 1.7*	2.19 ± .22*	61.8 ± 5.6*	29.0 ± 2.6*	−43.2 ± 7.3	85.7 ± 17.8	−38.7 ± 6.7
Control	10	17.9 ± .7	1.17 ± .08	97.2 ± 1.0	47.6 ± 1.0	−1.1 ± 2.6	0.1 ± 1.0	−0.8 ± 1.5
Enflurane								
Control	10	18.6 ± .9	1.15 ± .08	96.8 ± .8	47.2 ± 1.9	0	0	0
0.09	10	18.0 ± .9	1.44 ± .14*	87.9 ± .3*	44.1 ± 1.0	2.7 ± 3.8	17.8 ± 3.0	−5.4 ± 2.6
0.18	10	12.0 ± 1.7*	1.88 ± .18*	65.0 ± 6.1*	31.8 ± 1.4*	−35.4 ± 8.5	63.2 ± 10.8	−31.8 ± 4.0
0.24	5	8.6 ± 1.5*	2.03 ± .20*	53.0 ± 12.3*	32.4 ± 2.9	−50.9 ± 9.0	93.1 ± 12.4	−30.0 ± 9.2
Control	10	17.8 ± 1.3	1.23 ± .10	96.9 ± 1.3	46.0 ± 0.9	−5.4 ± 4.0	7.4 ± 5.4	−1.7 ± 4.2

Minimum alveolar concentration (MAC) doses of halothane and enflurane alone with duration of exposure are listed. The results of the digit span, choice reaction time, choice responses correct, and Purdue Pegboard Assembly are recorded as absolute values and as percent deviation from control.

*Significant when compared to control for that day ($p<0.05$).

TABLE 3
Amnesia Testing

Anesthetic agent	Word pairs (%)	Picture (%)
Halothane session		
Control	100(10/10)	100(10/10)
0.07 MAC	90(9/10)	100(10/10)
0.13 MAC	70(7/10)	100(10/10)
0.27 MAC	12(1/8)	75(6/8)
Control	100(10/10)	100(10/10)
Enflurane session		
Control	100(10/10)	100(10/10)
0.09 MAC	100(10/10)	100(10/10)
0.18 MAC	40(4/10)	70(7/10)
0.24 MAC	60(3/5)	60(3/5)
Control	100(10/10)	100(10/10)

The percentage of volunteers who remembered the word pairs or picture after each exposure is recorded in the columns, accompanied by the various fractions that comprised the calculated percentage.

ion (table 2, fig 1). Similarly, the choice reaction time increased significantly with increase in enflurane concentrations (fig 2). Response errors also increased in a dose-related fashion. The Purdue Pegboard Assembly control score averaged 47 pieces completed in 60 seconds, and this was unchanged during the 0.09 MAC enflurane exposure. The 0.18 and 0.24 MAC enflurane exposures significantly decreased the number of pieces assembled. However, only 5 volunteers completed the 0.24 MAC enflurane exposure and testing. No amnesia for word pairs or a picture was seen during the control exposure or the 0.09 MAC enflurane exposure (table 3). Both of the higher enflurane concentrations produced amnesia with word pairs again appearing to be most sensitive to anesthesia.

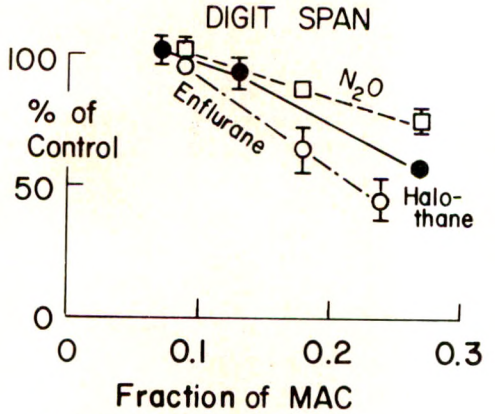


FIG 1. Enflurane, halothane, and N_2O all decrease the length of a sequence of numbers which can be remembered forward and backward. The effect is related to dose, and a threshold value of 0.05 to 0.1 MAC appears to be present for all 3 agents. The data for enflurane and halothane are from the present study. The N_2O data are from a separate study in which subjects were given N_2O 5, 10, 20, and 30%.[7] The 5% value is not shown since the results did not differ from those obtained at 10%. As indicated in the text, these 11 subjects had had more practice with the tests used (ie, were less naive) but otherwise were tested in the same fashion as the subjects in the present study.

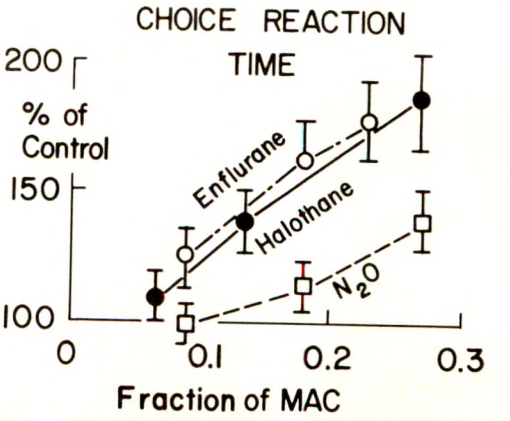


FIG 2. As with the digit span results, enflurane, halothane, and N_2O all increase choice reaction time in a dose-related fashion at concentrations exceeding 0.05 to 0.1 MAC.

DISCUSSION

Our results indicate that acute (half-hour) subanesthetic exposure to enflurane or halothane can impair mental performance and manual dexterity. The degree of impairment, as measured by the digit span, choice reaction time, and Purdue Pegboard increased as the concentration of either agent increased (fig 1 and 2). These results are qualitatively similar to those we previously found for N_2O[7] (fig 1 and 2) and halothane (fig 1 and 2). Some quantitative differences are apparent. Approximately twice the MAC concentration of N_2O is required to produce a given degree of choice reaction time impairment when compared to enflurane or halothane. However, we believe this relates to a difference in the groups of subjects. The volunteers given N_2O on a separate occasion received 0.1% alveolar halothane (0.13 MAC). In the present study, this concentration produced a 40% increase in reaction time but in the prior study only a 17% increase occurred—an increase comparable to that seen with N_2O. The difference between the groups may be explained by the naivete of the present group, which was significantly less practiced in taking the tests. Although a plateau in learning seems to occur (after an initial steep rise), further learning with practice may occur which makes subject capacity to perform more resistant to the effects of depressant drugs. Such an effect has been seen for marijuana.[9]

The upper limit of volunteer tolerance, ie, remaining conscious, appears to be 0.2 MAC, as demonstrated by the volunteers who could not complete the exposure and testing at the highest concentration of either enflurane or halothane. Both agents impaired function at concentrations which exceeded 0.05 to 0.10 MAC. That is, 5 to 10% of MAC appeared to be the threshold for change. These upper limits are associated with the development of significant verbal but not visual amnesia. This finding is in agreement with the work of Adam.[10]

Our results agree with the reports by Garfield et al[5] and Smith and Shirley.[6] However, the experiments by Bruce et al[2-4] produced results that differed from ours in that significant effects on behavior were seen at concentrations of halothane or enflurane which were 2 to 3 orders of magnitude less than those which produced no effect in our study (0.05 to 0.1 MAC). It is difficult to explain our failure to confirm their results. We used similar experimental instruments (choice reaction time and digit span). Differences did exist between our technics and those used by Bruce et al. In their testing for choice reaction time, the visual display consisted of a continuous line whereas ours was made up of dots. Their display changed from 1 of 4 possible forms to 1 of 2 of the remaining 3 possible forms; they did not change both the auditory and visual presentations concomitantly. We did. Their presentation of numbers for the digit span test was done verbally whereas ours was done visually. We believe that although these differences may have led to slight differences in the sensitivity of the test instruments, it is difficult to accept that the differences equaled an order of magnitude or more. Further evidence on this point comes from studies we have done on the effects of breathing nitrogen vs helium in volunteers (unpublished data). Using the same test instruments as in the present study, we found a significant difference. Furthermore, the magnitude of the difference was the same as that found earlier by Bruce's group for the same comparison.[11] This would suggest at least rough comparability of the sensitivity of the test instruments. As indicated above, our subjects were not completely naive and this may have decreased the sensitivity of their responses to depression. In contrast, Bruce's subjects in general were completely naive. The measurement of responses in our study was done by computer, thereby eliminating any potential for experimental bias. The administration of the tests by computer also eliminated experimental bias. This was not done in Bruce's study. Nonetheless, it is difficult to conceive of an unconscious bias producing the large changes found by Bruce's group. In summary, we have no convincing explanation for the differences found between our results and those of Bruce et al.

In conclusion, we have demonstrated significant dose-dependent impairment of mental function and manual dexterity at subanesthetic concentrations of halothane (0.1 to 0.2%) and enflurane (0.3 to 0.4%) in volunteers. We have documented amnesia in some of these volunteers during but not after anesthetic exposure. Volunteers become significantly impaired in minutes and recover quickly. The levels of anesthetics required to produce impairment far exceed those experienced by operating room personnel (eg, 0.001% halothane.)[1] However, such levels might be found for several hours in patients following prolonged anesthesia.

ACKNOWLEDGMENT

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JEJUNOILEAL BYPASS FOR OBESITY

One hundred and one carefully screened morbidly obese patients underwent jejunoileal bypass and were followed closely over a mean follow-up period of 32 months. Although there were no operative deaths, 3 patients died postoperatively of liver failure or its complications. A 4th patient died of a pulmonary embolus after reoperation, and the 5th patient died cachectic with severe diarrhea after excessive weight loss.

Nineteen percent of the patients required restoration of intestinal continuity (reversal), usually for either liver failure or late fluid and electrolyte derangements. All but 2 survived reversal and are doing well despite massive weight gain.

Fifty-eight percent of the patients had major complications which either required major reoperation (reversal, cholecystectomy, or incisional hernia repair) or were potentially life threatening (liver failure, hepatic fibrosis, or urinary tract stones).

As described in other series, abnormalities in serum electrolytes and vitamins were seen. In addition, hypovitaminosis D occurred in a number of patients and, as with other serum parameters measured, was time dependent in that improvement was seen in most patients over the postoperative interval studied.

Because of the high rate of complications and reversals, the authors believe that jejunoileal bypass should be reserved for patients with morbid obesity whose lives are imminently threatened by obesity or its sequellae. *(Halverson JD, Wise L, Wazna MF, et al: Jejunoileal bypass for morbid obesity: a critical appraisal. Am J Med 64:461-475, 1978)*

Anesthetic Considerations for Myasthenia Gravis and Pregnancy

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Three pregnant patients with myasthenia gravis are presented and anesthetic considerations discussed. The course of myasthenia gravis is highly variable and unpredictable during pregnancy. Anticholinesterase therapy should be maintained during labor, and the IM route of administration is preferred. Exacerbations very often occur in the immediate postpartum period. Regional anesthesia is preferred for vaginal delivery. In the case of cesarean section, general anesthesia may be preferable. Neonatal myasthenia gravis is a transient syndrome that appears in 20 to 30% of the newborns of myasthenic mothers.

Key Words—ANESTHESIA, obstetric. COMPLICATIONS, myasthenia gravis.

MYASTHENIA GRAVIS is a chronic disease characterized by weakness and easy fatigability of voluntary muscles that improves with rest and anticholinesterase therapy.[1] A major concern of the anesthesiologist is the frequent involvement of laryngeal, pharyngeal, and respiratory muscles. Patients with this disease may become pregnant and require anesthesia for vaginal or abdominal delivery or surgery during pregnancy. This paper reviews three cases and the problems that the myasthenic patient may encounter.

CASE ONE

A 33-year-old female weighing 55 kg presented to the delivery room at 1745 hours with fetal demise and chorioamnionitis. She had an 18-year history of myasthenia gravis and was taking pyridostigmine (Mestinon®) 120 mg orally 4 times a day and one 360-mg slow-release (Span) capsule orally at bedtime. Labor was induced with oxytocin (Syntocinon®) at 2030 hours. Since the patient had not taken her last 3 oral doses of pyridostigmine, 60 mg neostigmine was given orally at 2150 hours. At 2300 hours the patient's vital capacity was 500 ml. By 2340 hours her respirations were noted to be more diaphragmatic and she was having difficulty handling secretions. An additional 60 mg of neostigmine was given orally. The patient spontaneously delivered a fetus of less than 500 g at 0100 hours the next day. Immediately after delivery, she complained of difficulty breathing. Pyridostigmine 120 mg was given orally and the anesthesiologist

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was consulted. He administered neostigmine 2.0 mg and atropine 0.4 mg IV. Fasciculations occurred and the patient became apneic. Endotracheal intubation was performed and artificial ventilation started. Ninety minutes later vital capacity was 850 ml, the patient was awake and alert but had marked ophthalmoplegia, weakened tongue muscle movement, weak sternocleidomastoid function, and weak extremities. After a positive edrophonium (Tensilon®) test, a nasogastric tube was passed, through which the patient received pyridostigmine 60 mg. This was increased to 90 mg following a second positive edrophonium test. After 36 hours her forced vital capacity was 1700 ml. The endotracheal tube was removed and the patient had an uneventful recovery to her usual baseline level of strength. It was believed that this patient had a myasthenic crisis followed by a neostigmine-induced cholinergic crisis. The 2 mg of neostigmine which were administered represented approximately 4 to 8 times the recommended IV test dose.[2]

CASE TWO

The patient was a 34-year-old gravida 2, para 0, insulin-dependent diabetic who was admitted for elective cesarean section. Her first pregnancy resulted in a dead fetus delivered by cesarean section two years prior to admission. The patient also had a one-year history of myasthenia gravis manifested by a unilateral ptosis and diagnosed by a positive edrophonium test, but not requiring anticholinesterase therapy. The patient underwent an uneventful elective cesarean section with epidural anesthesia using 20 ml of 2% lidocaine. Both mother and baby had an uncomplicated hospital course.

CASE THREE

The patient was a 27-year-old female who had three uneventful pregnancies prior to the onset of her myasthenia gravis. She required treatment with 180 to 240 mg of pyridostigmine daily. One year following the onset of her myasthenia, she again became pregnant. During this pregnancy her pyridostigmine requirement increased 50%. She underwent vaginal delivery with spinal anesthesia using 4 mg of tetracaine. Mother and baby did well. Postpartum, the patient's pyridostigmine requirement decreased to prepregnancy levels.

DISCUSSION

Many patients suffering from myasthenia gravis have a benign intrapartum course but, as seen in our first patient, a life-threatening crisis may suddenly occur. It is therefore imperative that both the anesthesiologist and the obstetrician be aware of the implications of this disease in the pregnant patient.

Obstetrical Considerations

Influence of Pregnancy—The incidence of myasthenia gravis probably lies between 1:19,000 and 1:40,000,[2] and is twice as common in females. The age of onset is usually about 20 years. Therefore, pregnancy is not unusual among myasthenic patients. Pregnancy may influence the course of myasthenia gravis; also, the disease and drug therapy may affect labor, delivery, and the newborn.

The course of myasthenia gravis is highly variable and unpredictable in the antepartum period. Frenkel and Ehrlich[3] in 1964 introduced the concept that altered hormonal relationships in pregnancy may be responsible for the relapses of myasthenia gravis. They observed exacerbations of myasthenia in pregnancy and in the premenstrual phase of the reproductive cycle and suggested that progesterone was responsible for the deleterious effect of pregnancy. However, postpartum exacerbations are also very common[4] and the progesterone levels are falling at this time.

In 1958 Osserman[5] reported 25 patients with 36 pregnancies. In these patients 28% had no change in disease pattern, 40% had remissions, and 32% had a worsening of symptoms. Plauché[4] reviewed the intrapartum course in 87 patients with 126 pregnancies between 1938 and 1964 and found no consistent change in symptoms. Remissions and exacerbations occurred during the same pregnancy. The course during a previous pregnancy did not indicate what course the disease might take in future pregnancies. When exacerbations occur, they are most likely to happen in the first trimester[5,6] or in the postpartum period.[4,6] Induced abortion does not alter the course of the disease,[4,7-9] and exacerbation of symptoms is therefore not an indication for termination of pregnancy.

Whether pregnant or not, a myasthenic patient may present with a crisis, ie, marked muscle weakness and respiratory insufficiency. A frequent clinical problem is determining whether the patient has received too little anticholinesterase therapy and is in a myasthenic crisis, or too much anticholin-

esterase medication and is in cholinergic crisis. It is often difficult to distinguish between the two conditions.

Several pharmacological tests may be used to determine whether a patient needs more or less anticholinesterase therapy. Edrophonium administration is a safe and widely used test of the adequacy of anticholinesterase therapy.[10] The patient's muscular strength is first assessed objectively (eg, vital capacity, grip strength, ability to chew, or presence of ptosis). Muscle strength then is reassessed 30 to 90 seconds after a test dose of 2 mg of edrophonium is given IV. If no deterioration is detected, an additional 8 mg is given IV.[11] If there is difficulty in interpreting the results, a placebo injection of saline is then given. The effect of edrophonium wears off rapidly, and the test can be repeated in 10 minutes if results are equivocal. In inadequately medicated patients, muscle strength dramatically improves. In overmedicated patients, muscle strength does not change or may worsen slightly.

The neostigmine test and curare test which were previously used in the diagnosis of myasthenic emergencies have been replaced by the edrophonium test. For further details on these tests, the reader is referred to review articles by Foldes,[10] Foldes and McNall,[2] and McNall and Jafarnia.[12]

The use of anticholinesterase drugs for diagnosis or therapy of myasthenia gravis has a potential hazard during pregnancy because stimulation of uterine cholinergic receptors may increase uterine tone and contractility. This suggests that myasthenic patients receiving anticholinesterase therapy and therefore having higher levels of acetylcholine would have an increased incidence of spontaneous abortions or premature labors. An early study of Osserman[5] did in fact demonstrate this but a recent larger series demonstrated no increase in the abortion rate.[4]

Anticholinesterase drugs given IV may also directly stimulate acetylcholine release.[13] This is especially true in late pregnancy.[2] Thus, several authors have recommended that the standard edrophonium test for myasthenia should be avoided during pregnancy, and IV neostigmine therapy administered with extreme caution, lest premature labor be precipitated. In these circumstances IM neostigmine (0.5 mg/45 kg) is suggested.

A myasthenic crisis may be precipitated by emotional stress, by exertion, or by minor upper respiratory or urinary tract infections. Indeed, our first patient had the emotional stress of a stillbirth combined with the physical stress of chorioamnionitis. Antibiotics must be selected carefully since many have muscle-relaxing properties. These include neomycin, streptomycin, gentamycin, kanamycin, polymixin, colistin, tetracycline, and lincomycin.[14] Some of the aminoglycosides listed above have been reported to exacerbate myasthenic symptoms.[15] Penicillin, erythromycin, and chloramphenicol do not have neuromuscular blocking properties.[14]

Labor and Delivery—Myasthenia does not affect the course of labor and is not an indication for cesarean section. In the largest reported series of pregnant women with myasthenia gravis, the cesarean section rate was 5.7%.[4] However, outlet forceps frequently are used to shorten the second stage of labor and thereby minimize muscle fatigue associated with expulsive efforts.

Magnesium sulfate is commonly used in the therapy of pre-eclampsia during labor. However, magnesium therapy may be contraindicated in the presence of myasthenia gravis.[16] Magnesium may produce a neuromuscular block by decreasing the amount of acetylcholine released at the motor nerve terminal and depressing the excitability of the muscle membrane.[17] The myasthenic patient is particularly sensitive to the effects of magnesium[16] and muscle weakness, and respiratory insufficiency may follow administration of magnesium to a pre-eclamptic myasthenic patient.

Anticholinesterase therapy must be maintained during labor. Because of unreliable gastric uptake of all drugs during this period, it is recommended that oral administration be discontinued at the onset of labor and IM equivalents be substituted.[2,9,10] (table).

The Postpartum Period — The first 10 postpartum days may be especially hazardous. Plauché reported that 57% of patients had exacerbation of symptoms and 2.4% (3 patients) died from myasthenic crises during this period.[4] The patient's normal oral medication should be resumed as soon as possible and her disease status should be monitored carefully for at least 10 days, preferably in the hospital. During this period, intermittent edrophonium tests are

TABLE
Equivalent Doses of Commonly Used Anticholinesterases

Drug	IV dose (mg)	IM dose (mg)	Oral dose (mg)
Neostigmine (Prostigmin®)	0.5	0.7-1.0	15.0
Pyridostigmine (Mestinon®)	2.0	3.0-4.0	60.0

useful in determining if the patient is receiving appropriate anticholinesterase therapy.

It is not clear whether breast feeding exacerbates symptoms.[12,18] Insofar as the neonate is concerned, breast feeding is not contraindicated because anticholinesterase drugs are not transmitted in detectable amounts into breast milk.[12]

Anesthetic Considerations

Preanesthetic Assessment—Ideally, an anesthesiologist should visit all patients prior to the onset of labor; it is mandatory that he visits with all myasthenic patients prior to the onset of labor. In addition to the usual anesthetic assessment, information concerning myasthenic symptoms and therapy should be obtained. Physical examination should include particular attention to respiratory and bulbar involvement. Hemoglobin, serum electrolytes, and proteins may be abnormal if the patient has bulbar weakness sufficient to compromise adequate nutrition. An ECG is recommended because focal necrosis of the myocardium may occur.[19,20] Myasthenia gravis is frequently associated with hyperthyroidism, and thyroid-function studies are recommended if there is clinical suspicion of thyroid dysfunction. Recently performed pulmonary function tests will be of value in managing severe respiratory insufficiency, should it develop.

Anesthesia for Vaginal Delivery—Since myasthenic patients may have marginal respiratory reserve, it is recommended that all tranquilizers and narcotics be administered in less than the usual doses to avoid possible retention of secretions or respiratory depression.[21] The proposed mechanism of action of these drugs may not simply be a depression of ventilation in a weak patient since it is known that high doses of morphinelike drugs block neuromuscular transmission.[22] For vaginal delivery, regional anesthesia is preferred by many.[2,10,12,18]

Low spinal or epidural anesthesia to a T-10 level during labor will decrease the requirements for systemic medications, prevent fatigue, and allow the use of outlet forceps to shorten the second stage of labor. Foldes[10] recommended spinal anesthesia over other regional technics which require larger doses of local anesthetic drugs because high blood levels of local anesthetics may interfere with neuromuscular transmission.[23,24] However, the effects of systemic blood levels of local anesthetics by themselves on neuromuscular transmission only become significant at levels which cause death in experimental animals.[24] In addition, it is known that local anesthetics given in antiarrhythmic doses can enhance neuromuscular block from both depolarizing and nondepolarizing muscle relaxants[24,25] and result in respiratory depression. The effects on the neuromuscular junction are small and insignificant and the primary cause of respiratory depression is central nervous depression by the local anesthetic agents.[25] There is no evidence of increased sensitivity of the neuromuscular junction of patients with myasthenia gravis to local anesthetic drugs. This is illustrated by the fact that our second patient received 400 mg of lidocaine without any untoward effects. Epidural anesthesia has previously been used safely for vaginal delivery in myasthenics.[18,26]

Chloroprocaine, an ester-type local anesthetic, has recently gained widespread popularity in obstetrics. The drug is rapidly hydrolized by maternal plasma cholinesterase, and placental transfer is minimal. However, in the myasthenic patient on anticholinesterase therapy, plasma cholinesterase activity is significantly decreased[27] and maternal and fetal toxicity may be enhanced. On this theoretical basis, therefore, chloroprocaine, as well as tetracaine, another popular ester-type local anesthetic, is not recommended for epidural anesthesia. Tetracaine may be used for spinal anesthesia because only small doses are necessary. There is no evidence that the metabolism of amide-type drugs is altered in myasthenia gravis.

During labor, vital capacity determinations should be performed at frequent intervals to detect as early as possible the onset of respiratory insufficiency. Progressive decrements in a series of three consecutive vital capacities indicate easy fatigability. Anticholinesterase therapy may require adjustment during labor because of varying physical exertion and emotional status. It has been recommended that IM administration

be so timed that a dose is given one-half hour before delivery to assure maximum maternal strength.[5]

Occasionally, vaginal delivery may require a general anesthetic with or without uterine relaxation. Thiopental and other short-acting barbiturates can be used safely. Although mask induction of anesthesia using N_2O, O_2, and halothane is often recommended for myasthenic patients, this technic is not suitable in the obstetric patient with a potentially full stomach. Awake endotracheal intubation, or rapid thiopental induction with immediate intubation, often is easily accomplished in the myasthenic patient without additional agents. However, to facilitate rapid intubation, muscle relaxants may be required. Since myasthenics are more sensitive to nondepolarizing relaxants, the usual pretreatment with curare prior to succinylcholine to prevent muscle fasciculations and increased intragastric pressure should be avoided. However, some clinicians recommend 2 to 3 mg of curare without subsequent succinylcholine to provide the necessary muscle relaxation for rapid endotracheal intubation.[28] In patients with myasthenia gravis a low dose of curare will have rapid onset and an exaggerated response. Since redistribution and excretion of curare are the same as in normal patients, however, the duration of action is similar. The use of succinylcholine in myasthenia gravis is controversial since noninvolved muscles are resistant and involved muscles are more sensitive.[10] A dose of 30 to 50 mg usually provides suitable conditions for endotracheal intubation; however, duration of paralysis may be prolonged up to 90 minutes due to the anticholinesterase therapy.[29]

If uterine relaxation is necessary, halothane may be used. Commonly used volatile agents such as halothane and enflurane are known to potentiate the neuromuscular blocking actions of muscle relaxants.[30,31] The anesthetist should control the myasthenic patient's ventilation during general anesthesia.

Anesthesia for Cesarean Section—While regional anesthesia may be used safely for cesarean section, special consideration should be given to the combined effects of a high motor block and pre-existing respiratory impairment. Patients with ocular myasthenia or with mild generalized myasthenia not involving the respiratory muscles are suitable candidates for spinal or epidural anesthesia. Patients with bulbar or respiratory muscle involvement should be given endotracheal anesthesia unless they are well controlled with anticholinesterase therapy. If regional anesthesia is used and the level of motor blockade compromises normal ventilation or clearance of secretions, general endotracheal anesthesia should be instituted.

The myasthenic patient seldom requires a muscle relaxant during maintenance of general anesthesia. If needed, 0.5- to 1.0-mg increments of curare may be used, with response monitored by a nerve stimulator. During reversal of nondepolarizing relaxants with IV increments of neostigmine 0.5 mg or pyridostigmine 1.0 mg, twitch height and tetanus should be monitored lest a cholinergic crisis be precipitated. Indeed, some advise against reversing the block and prefer to ventilate the patient until neuromuscular function spontaneously recovers fully.[21] It is usually possible to reverse the muscular blockade and to extubate the patient if the patient's disease is stable and well controlled preoperatively.

Postoperative Care — Postoperative morbidity and mortality most frequently relate to respiratory and circulatory complications and to overzealous anticholinesterase therapy.[2] Anticholinesterase requirements vary widely in the immediate postpartum period and must be assessed by repeated measurements of vital capacity and by response to edrophonium. Meticulous respiratory care includes adequate ventilatory support and, if necessary, endotracheal suctioning and chest physical therapy. Circulatory instability may result from myocarditis, which may be associated with myasthenia. These patients require intensive care for at least 48 hours postoperatively.

Congenital and Neonatal Myasthenia Gravis

Newborn infants may suffer from myasthenia gravis. Congenital myasthenia gravis, a chronic illness which may appear at birth in the newborns of normal mothers, has a course similar to that observed in adults.[10] In addition, neonatal myasthenia gravis may occur transiently in 20 to 30% of babies born to mothers with myasthenia. It usually presents with generalized muscle weakness and an expressionless face.[10,12] Eighty per cent of cases begin within 24 hours of birth,[32] with the latest reported onset at 3 days. Anticholinesterase transfer across the placenta may explain the delayed onset after birth[26] but transfer of such highly ionized drugs has not been demonstrated.

The anesthesiologist may be called on to assess myasthenic neonates in the delivery room or in the nursery. Sucking, swallowing, and breathing may be impaired even in mild cases. When respiratory efforts are inadequate, the newborn should be intubated and ventilated and then diagnostic tests undertaken. Neonatal myasthenia may be confirmed by the rapid clinical improvement following 0.5 to 1.0 mg edrophonium IM or subcutaneously. Intramuscular anticholinesterase therapy, neostigmine, 0.05 to 0.1 mg, or pyridostigmine, 0.1 to 0.4 mg, can be given every 4 hours following confirmation of the diagnosis.[8]

Infants born of myasthenic mothers who show evidence of transient myasthenia themselves usually recover in a few weeks. Anticholinesterase therapy is generally needed for about 21 days, with a maximum of 47 days.[32] As the baby's strength improves, anticholinesterase dosage should be reduced. Improvement is permanent in most cases. However, one case of a recurrence has been reported.[32] In addition, one case of neonatal myasthenia was completely cured after an exchange transfusion for hyperbilirubinemia on the second day of life.[26] Further investigation of this phenomenon may provide some insight into the pathogenesis of neonatal myasthenia gravis.

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PULMONARY WEDGE PRESSURE MEASUREMENT

Changes in the mean pulmonary wedge pressure were measured during temporary disconnection from the ventilator in 29 patients to assess the effects of therapy with controlled ventilation on determinations of pulmonary wedge pressure. In 16 observations during use of intermittent positive-pressure ventilation, the mean value for the pulmonary wedge pressure was the same (10.3 mm Hg) with the patients connected to or disconnected from the ventilator. Thirteen patients were also maintained on positive end-expiratory pressure (PEEP, range 5 to 10 cm H_2O); the mean ($\pm$ SD) of 17 measurements of pulmonary wedge pressure was not significantly different on cessation of mechanical ventilation (12.5 $\pm$ 6.7 mm Hg vs 11.7 $\pm$ 6.9 mm Hg). These data indicate that pulmonary wedge pressure can be measured accurately at the end of exhalation during the administration of positive-pressure ventilation with 10 cm H_2O of PEEP. The suggested practice of discontinuing mechanical ventilation in order to obtain a more exact measurement is not warranted. *(Davison R, Parker M, Harrison RA: The validity of determinations of pulmonary wedge pressure during mechanical ventilation. Chest 73:352-355, 1978)*

Local Anesthetics and Tracheal Ring Ciliary Activity

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The effects of local anesthetics on ciliary activity were studied using ferret tracheal rings maintained in vitro. Ciliary activity was quantitated visually after exposure to varying concentrations of mepivacaine, lidocaine, procaine, chloroprocaine, and bupivacaine. The recovery of ciliary activity was determined after tracheal rings were washed free of the local anesthetic agent. Mepivacaine was the least toxic, with no effect on ciliary activity at a 1.0% concentration. Bupivacaine was the most toxic, with irreversible damage to respiratory epithelium at a concentration of 0.13%. Lower concentrations caused ciliostasis, with some recovery after removal of the anesthetic. Lidocaine, procaine, and chloroprocaine also depressed ciliary activity which, in general, was reversible after removal of the anesthetic.

Key Words—LUNG, tracheal cilia. ANESTHETICS, local, mepivacaine. ANESTHETICS, local, procaine. ANESTHETICS, local, lidocaine. ANESTHETICS, local, bupivacaine. ANESTHETICS, local, chloroprocaine.

ENDOSCOPIC examinations of the upper respiratory tract are usually done under topical anesthesia. A number of local anesthetics are available and several studies have compared their cytotoxicity.[1-5] In most of these studies, the acute effects of various agents on ciliary activity of excised strips of trachea from experimental animals were studied.[6-10] In attempts to document longer term effects, tissue cultures of respiratory epithelium, prepared by teasing out cells from trachea of animals, were exposed to various agents and the ciliary activity estimated visually or cinemicrophotographically. However, in these tissue culture models it was not possible to study long-term effects on the ciliated epithelium after removal of the anesthetic[2,3,10] as only the anesthetic concentration which caused acute ciliostasis was examined.

Recently, organ cultures of tracheal rings have been used to study the effects of respiratory viruses on respiratory epithelium.[11] This technic preserves the integrity of the respiratory epithelium. Additionally, the organ culture can be maintained for prolonged periods. Using ferret trachea in organ culture, we studied acute and chronic effects of mepivacaine, lidocaine, procaine, chloroprocaine, and bupivacaine on the respiratory epithelium.

MATERIALS AND METHODS

Organ Culture—The organ culture method is a modification of the technic described by Hoorn and Tyrrell.[11] The ferret possesses a long neck, and 100 or more tracheal rings could be obtained from a single ferret. Following an overnight fast, ferrets were given a lethal dose of sodium thiopental intraperitoneally and exsanguinated by cardiac puncture. The skin was washed with alcohol and, under strict sterile operative procedures, an incision was made circumferentially at the level of the umbilicus. While an assistant held the pelvis under the sterile drapes, the upper skin edge was everted and pulled cephalad over the head. This maneu-

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ver of everting the skin provided a sterile, fur-free environment over the neck and thorax. The trachea was isolated below the thyroid cartilage to the carina by blunt, bloodless dissection; transected; and placed in a sterile screw-top tube containing L-15 tissue culture medium.[12] This is a special medium containing many amino acids with different pK_a values. Thus, this medium does not require gassing with CO_2 or any buffers and is responsible for the prolonged survival of the tissues.

Beneath a sterile hood maintained by ultraviolet light and bacteria-filtered laminar air flow, the excised trachea was transferred after flaming the screw-top tube onto a Petri dish supported on a plastic platform containing a light source. All adherent connective tissues were carefully dissected, and complete rings were prepared by cutting transversely between the tracheal cartilages. The rings were carefully transferred to sterile screw-top tissue culture tubes (Flow Laboratories, Rockville, Maryland), one ring per tube, containing 1 ml of L-15 medium, to which L-glutamine (1% final concentration), 100 units of penicillin, and 20 μg gentamicin had been added. Tubes were then rolled in a tissue culture rotator at 37 C at 8 revolutions per hour. This provided a gas-liquid interface which also contributed to the prolonged survival of the ciliated epithelium. The ciliated epithelium of the tracheal rings regularly survived for periods of 30 to 50 days and occasionally up to 90 days. The rings tend to adhere to one side of the tube and remain in position if undisturbed. To prevent accumulation of debris in the center of the ring, thus obscuring the cilia, the tubes were shaken gently each day.

Grading of Ciliary Activity—The screw-top tubes were removed from the tissue rotator and placed in a water bath at 37 C while waiting to be examined. The ciliary activity was graded by determining the percentage of cilia beating on each ring, using transmitted light and the 10× objective of an inverted microscope. Although differences in the vigor and speed with which the cilia beat were observed, only gross changes of presence or absence of ciliary activity were utilized in this comparative study. After quick observation of the entire ciliary epithelium of the ring, a prominent "landmark" on the epithelium was located. From this point, the number of microscopic fields required to scan the entire epithelium was determined. For example, if 8 fields were required to scan the entire ring, each field represented 12.5% of the entire epithelium. If all the fields showed ciliary activity, it was scored as 100%. If ciliary activity was absent, the score was zero. However, if only 3½ fields showed ciliary activity, the ring was scored as 44%. With experience, the percentage of ciliary activity could be determined rapidly. All readings were made by the same observer (SRM). After preparation of the rings, there was a definite improvement of the ciliary activity over the first 24 to 72 hours. Also, during this period the traumatized cells were shed and so, under the sterile hood with sterile procedures the medium was removed in order to remove the cellular debris and excess mucus. Therefore, baseline data were not obtained until 72 hours following preparation of the rings.

Exposure to Local Anesthetics — Sterile ampules of local anesthetic agents were diluted with L-15 medium to provide a range of concentration. One millilitre of each dilution of the local anesthetic was added to the screw-capped tubes containing the tracheal rings under a sterile hood. One millilitre of L-15 medium was added to the control tubes. To determine the effect on ciliary activity, each dilution of the local anesthetic or L-15 medium (control) was added to 4 screw-capped tubes, which formed a group.

The mean percentage ciliary activity of each group was determined before and 10, 30, and 60 minutes after the local anesthetic was added. Following the 60-minute reading, the medium was removed and fresh medium (1 ml) added. The mean percentage ciliary activity was again determined 10 minutes and 16 hours following the removal of the local anesthetic.

Experimental Design—The percentage of actively beating cilia on each ring was recorded on the day of the experiment after which the medium was changed. The tubes were arranged according to their percentage activity. Each experimental group consisted of 4 tubes. The allocation of the tubes was such that each experimental group had an equal number of tubes with the high and low percentages of ciliary activity and their mean percentage ciliary activity was similar.

RESULTS

The ciliary activity was recorded as an all-or-none phenomenon and correspondingly scored zero or 100%. The intermediate scores were within 10% error, and only the

zero and 100% scores were taken in comparing their ciliotoxicity.

As shown in the table, mepivacaine caused no reduction in ciliary activity at concentrations from 0.13 to 1.0%. In contrast, bupivacaine was very toxic to tracheal rings. Thirty minutes after exposure to 0.03% bupivacaine, the lowest concentration tested, no cilia were beating. After washing tracheal rings free of bupivacaine some recovery of ciliary activity was seen in the 0.03 and 0.06% concentrations. Concentrations as low as 0.13% caused cell death and desquamation of the respiratory epithelium.

A 2.0% concentration of lidocaine caused rapid inhibition of ciliary activity and by 30 minutes cilia were completely stopped. This effect was not reversed after washing. A 1% concentration of lidocaine paralyzed cilia, but this effect was partially reversible 10 minutes after washing. A 0.5% concentration of lidocaine caused some impairment of ciliary activity, but this was completely reversible. Lower concentrations of lidocaine (0.25 and 0.13%) had no effect.

Procaine and chloroprocaine were similar to lidocaine. With 0.5% and 0.7% respectively, ciliostasis without recovery was noted, whereas with 0.25% and 0.40% paralysis was followed by full recovery. Concentrations of 0.06% and 0.20% respectively had no effect.

DISCUSSION

In comparing the toxicity of local anesthetics, the absolute toxicity is of little importance to the clinician who is primarily concerned with toxicity at equianesthetic concentrations. Therefore, corrected toxicity ratio (ie, relative toxicity/relative anesthetic, using procaine as the standard of reference[13-15]) was utilized to determine the equianesthetic concentrations. When local anesthetics were compared as described previously, bupivacaine was the most toxic of the drugs tested, causing cell death and desquamation of the respiratory epithelium. Even at low concentrations, bupivacaine caused ciliostasis, while mepivacaine, at a 1.0% concentration, had no effect on ciliary activity.

The concentrations of lidocaine and procaine which inhibited ciliary activity were lower than the 5.0% value previously reported by Corssen and Allen.[3] Corssen and Allen also reported that 0.5% chloroprocaine inhibited cilia, which is in agreement with our results, and observed stimulation of ciliary activity at 0.1% concentrations of lidocaine and procaine, which was not observed in our studies. These discrepancies are probably methodologic, since these authors utilized punch biopsies of human respiratory epithelium in tissue cultures and recorded their rotations cinemicrophotographically. The speed of rotation was then related to the ciliary activity. However, the speed of rotation of a clump of cells depends upon the weight of the cell cluster, integrity of the ciliated epithelium, mucus, and the viscosity of the medium, all of which are difficult to standardize.

A major advantage of the organ culture we used is that the integrity of the respiratory epithelium is maintained. Also, use of L-15 medium consisting of a combination of a number of amino acids with different pK_a values obviates the necessity to use buffers and CO_2 gassing of the cultures. Further, use of a tissue culture rotator exposing the tracheal rings to a gas-liquid interface, in contrast to being completely immersed in the tissue culture medium all the time, greatly prolonged the survival of the tissues.

The respiratory epithelium synthesizes choline esterase and choline acetylase.[16] Therefore, procaine and chloroprocaine, which are degraded by esterase enzymes, were initially expected to be less toxic than the amide group of local anesthetics. However, the amide anesthetic mepivacaine was the least toxic agent studied and no correlation could be found between toxicity and the chemical structure of the local anesthetics tested. On the other hand, the duration of action of the local anesthetics appeared to be associated with ciliostasis since the most toxic of the local anesthetic agents was bupivacaine, which was also the longest acting agent tested.

Currently, bronchoscopy is performed under topical anesthesia. Since some local anesthetics impair ciliary activity, their use might diminish pulmonary clearance.[17] Since mepivacaine was the least toxic of the agents studied, it would appear to be superior to lidocaine and deserves additional evaluation. Because of the toxic effects of bupivacaine, even at low concentrations, it should not be used.

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TABLE

Ciliary Activity of Tracheal Rings in Organ Culture Exposed to Mepivacaine, Lidocaine, Procaine, Chloroprocaine, and Bupivacaine

Effective anesthetic concentration (%)†	Mepivacaine*					Lidocaine*					Procaine*					Chloroprocaine*					Bupivacaine*				
	Acute exposure (min)			Recovery phase		Acute exposure (min)			Recovery phase		Acute exposure (min)			Recovery phase		Acute exposure (min)			Recovery phase		Acute exposure (min)			Recovery phase	
	10	30	60	10 min	16 hr	10	30	60	10 min	16 hr	10	30	60	10 min	16 hr	10	30	60	10 min	16 hr	10	30	60	10 min	16 hr
2.0						19	0	0	0	0															
1.4																0	0	0	0	0					
1.0	100	100	100	100	97	67	3	0	47	55															
0.7																0	0	0	0	0					
0.5	100	100	100	100	98	96	74	53	93	99	2	0	0	0	0						0	0	0	0	0
0.40																100	100	6	93	100					
0.35																									
0.25	100	100	100	100	100	100	99	98	97	100	83	47	7	91	88						21	0	0	0	0
0.20																100	100	100	100	97					
0.13	100	100	100	100	99	100	100	100	100	100	95	91	70	93	87						23	0	0	0	0
0.06											100	100	100	98	94						31	0	0	84	100
0.03																					41	0	0	27	86
Control	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

*Mean ciliary activity (%)

†Calculated from corrected toxicity ratios[13-15]

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PAIN TREATMENT IN HERPES ZOSTER

Varicella virus infection of sensory nerve ganglia causes herpes zoster. Twelve cases of cutaneous herpes zoster were treated with epidural injections of 0.25% bupivacaine and methylprednisolone acetate. Single-injection thoracic or lumbar epidural blocks were used in 3 patients. Nine patients had a series of 3 lumbar epidural blocks on successive days. Treatment was effective for herpes zoster of less than 7 weeks' duration. The course of herpes zoster of greater than 3 months' duration (postherpetic neuralgia) was not improved. The administration of epidural bupivacaine plus methylprednisolone acetate was no more effective than when bupivacaine alone was used. Epidural injection of bupivacaine with or without methylprednisolone acetate is the treatment of choice for the pain of cutaneous herpes zoster in its early stages. *(Perkins HM, Hanlon PR: Epidural injection of local anesthetic and steroids for relief of pair secondary to herpes zoster. Arch Surg 113:253-254, 1978)*

Blood Pressure in the Great Toe with Simulated Occlusion of the Dorsalis Pedis Artery

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Blood pressure was measured in both great toes using strain-gauge plethysmography in 100 healthy persons aged 18 to 43 before and during successive compression of the dorsalis pedis artery, the posterior tibial artery, and both arteries at the same time. In 54 (27 percent) of 200 feet, successive compression of the dorsalis pedis and the posterior tibial arteries produced no decrease in pressure in the great toe. In 47 of the feet, toe pressure decreased significantly only after compression of the posterior tibial artery, and in 65 of the feet toe pressure decreased significantly only after compression of the dorsalis pedis artery. In 34 of the feet, toe pressure decreased significantly after compression of each of the arteries. Thus in 99 (50 percent) of 200 feet, compression of the dorsalis pedis artery decreased the pressure in the great toe significantly, and in 4 feet the pressure decreased below 40 mm Hg. When both arteries were simultaneously compressed, 69 feet showed detectable blood pressure in the great toe. Attempts to evaluate adequacy of collateral circulation by pressure blanching of the great toe prior to artery compression and then observing capillary refilling time upon release of toe compression proved unreliable.

Arterial cannulation of the dorsalis pedis should not be routinely performed since collateral circulation may prove inadequate should the artery be thrombosed, unless blood pressure is measured beforehand in the toes before and following manual occlusion of the dorsalis pedis artery.

Key Words — ARTERIES, dorsalis pedis. MONITORING, vascular. ANATOMY, dorsalis pedis artery.

CANNULATION of the dorsalis pedis artery is 1 of the technics available when intra-arterial blood pressure monitoring or frequent arterial samples for blood-gas determinations are needed. However, little is known about the potential risks of cannulating this artery. Spoerel et al[1] demonstrated with Doppler-flow studies that the main arterial supply to the toes comes from the dorsalis pedis artery in approximately 16 percent of cases. Youngberg and Miller[2] performed 30 percutaneous cannulations in cases where posterior tibial arterial flow was considered adequate as judged by Doppler-flow studies. They found a 6.7 percent incidence of thrombosis following cannulation of the doralis pedis artery. This suggests that before cannulation of the dorsalis pedis artery the consequences of an occlusion of the artery be evaluated by determination of the existence of sufficient collateral flow through the posterior tibial artery, the peroneal artery, and the malleolar network. Johnstone and Greenhow[3] suggested that this could be done by occluding the dorsalis pedis artery, blanching the great toe by compression of the toenail and pulpa, and then observing the rapidity of the capillary refilling after releasing the compression of the toe.

We have evaluated the importance of the various arterial contributions to the maintenance of the distal blood pressure in the normal foot as part of a study of the feasibility of cannulation of the dorsalis pedis artery.

MATERIAL AND METHODS

One hundred healthy volunteers (61 females and 39 males) were examined. Their ages ranged from 18 to 43 years, with a median age of 28.7 years. Age distribution was the same in females and males, median

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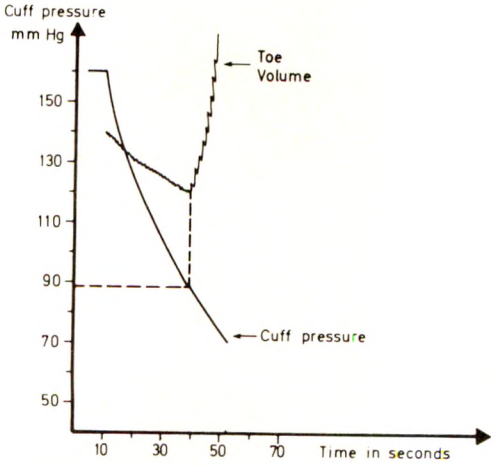


FIGURE. Cuff pressure and plethysmographic recording during measurement of blood pressure. Vertical dotted line is the projection of "deflection point" on the pressure recording. Horizontal dotted line is the reading of this pressure on the ordinate.

ages being 27.5 and 30.0 years, respectively. Blood pressure in the great toe was determined using a method based on the conventional pneumatic cuff principle. A 22-mm-wide cuff was placed around the proximal phalanx of the great toe. Blood passing under the cuff was detected by plethysmography, the volume detector being a mercury-in-rubber strain gauge (Parks Electronics, Oregon) placed around the distal phalanx of the great toe. After inflation of the cuff to about 30 mm Hg above systolic blood pressure, the pressure in the cuff was slowly released until an increase in the intravascular volume of the toe was observed on the strain gauge plethysmograph, indicating that pulse waves were passing the cuff; the cuff pressure at this point indicated the perfusion pressure of the toe. A typical plethysmographic recording is shown in the figure. For more detailed information about the method, the reader is referred to the monograph by Gundersen.[4]

The examination was performed with the subjects in the supine position. In each foot, the dorsalis pedis artery was 1st compressed, then the posterior tibial artery, and finally both arteries were compressed simultaneously. The blood pressure was measured after each compression. Compression of both arteries simultaneously reflects collateral flow through the peroneal artery and the malleolar network. Using a 2-channel strain gauge, blood pressure in the great toe was determined simultaneously on both sides. A decrease in systolic pressure greater than 10 mm Hg (2.5 times the SD on double determinations; see Gundersen[4]) was taken as evidence that arterial occlusion was followed by a significant reduction in perfusion pressure of the great toe. For purposes of analysis, the decrease in blood pressure in the toe after compression of 1 or both arteries was expressed as percent of the pressure prior to compression. All subjects were investigated at a constant room temperature of 22° C.

Physical examination was also performed in all persons as follows: With the person supine, the dorsalis pedis artery was compressed and the great toe blanched by compressing the toenail and pulpa. After 30 seconds the compression of the toe was released and capillary refilling observed. If the refilling was complete within 10 seconds, the test was regarded as negative and adequate collateral flow was assumed to exist.[3] All examinations were performed by the authors.

Statistical Methods—As the variables in the material could not be assumed to follow a normal distribution, they were described by median and range. Quantitative variables were compared by Wilcoxon's test for unpaired data, while binary data were compared by the χ^2-test with Yates's correction.

RESULTS

The posterior tibial artery was palpable in all 200 feet. In 4 feet (in 3 persons) the dorsalis pedis artery was not palpable.

In 54 feet no decrease in blood pressure in the great toe occurred after compression of either the dorsalis pedis or the posterior tibial artery. In the remaining 146 feet, compression of 1 of the 2 arteries was followed by a decrease of blood pressure in the great toe, ie, perfusion pressure through collaterals was inadequate to fully compensate for the decrease in flow produced by arterial occlusion. The results are shown in the table.

In 47 feet, the blood pressure in the great toe was reduced after compression of the posterior tibial artery but not after compression of the dorsalis pedis artery. In 65 feet, the blood pressure was reduced after compression of the dorsalis pedis artery but not after compression of the posterior tibial artery. In the remaining 34 feet, a decrease in blood pressure in the great toe occurred after compression of the dorsalis pedis artery *and* after compression of the posterior tibial artery. Thus, in 99 feet (49.5 percent), compression of the dorsalis pedis artery was

TABLE
Results Following Compression of Dorsalis Pedis and Posterior Tibial Arteries in 100 Healthy Persons

Artery compressed	Feet with decreased pressure		Magnitude of decrease in pressure	
	No.	%	Range, %	Median values
Following comp. of d.p.a. but not p.t.a	65	32.5	9 - 41	27.2
Following comp. of p.t.a. but not d.p.a.	47	23.5	9 - 100	30
Following comp. of d.p.a. and following comp. of p.t.a.	34	17	d.p.a. 12 - 44 p.t.a. 12 - 91	20 26
Total following comp. of d.p.a.	99	49.5	9 - 44	23.8
Total following comp. of p.t.a.	81	40.5	9 - 100	29.7

Decrease in blood pressure in the great toe is shown as percent of pressure in the great toe prior to compression.
Comp. = compression
P.t.a. = posterior tibial artery
D.p.a. = dorsalis pedis artery

followed by a decrease in blood pressure in the great toe. Dorsal pedis artery compression resulted in a pressure below 40 mm Hg in 4 feet (in 3 persons), 2 percent of all cases.

In 131 feet (65 percent), there was no detectable toe blood pressure after simultaneous compression of both arteries.

When both the dorsalis pedis and the posterior tibial arteries were simultaneously compressed, only 18 feet in 9 females (14.8 percent of 61 females tested) showed detectable blood pressure in the great toe. Corresponding values in males were 51 feet in 27 men (65.4 percent of 39 males tested), the difference between females and males was statistically highly significant ($p<0.001$).

We found the capillary refilling test extremely difficult to evaluate, especially when the feet were cold. The test was not clearly positive in the 196 feet where the dorsalis pedis artery was palpable.

DISCUSSION

Earlier studies have indicated that in 3 to 14 percent of subjects the dorsalis pedis artery cannot be palpated.[5-7] Indeed, anatomical studies have shown the dorsalis pedis artery to be absent in 3 to 12 percent of cases.[8] In the present study, on the other hand, absence of a palpable dorsalis pedis artery was found in only 2 percent of cases (confidence limits, 0.6 to 5 percent).

Previous evaluations of the flow through the arteries of the foot have usually relied upon the Doppler flow principle alone.[1,2] This is a qualitative technic which can detect whether or not a flow is present. We have chosen to measure the blood pressure in the great toe in order to quantitate changes following arterial compression. By combining strain-gauge plethysmography with a pneumatic cuff technic, systolic pressures from 200 to 10 mm Hg can be determined.

The reproducibility of the strain-gauge method for measuring blood pressure in digits has been described in several studies,[9,10] showing a standard deviation on double determinations of 4 mm Hg when the systemic pressure is unchanged and when the cuff and strain gauge are not disturbed between determinations. In the present study we regarded pressure changes exceeding 10 mm Hg (2.5 times the SD on double determinations) to be statistically significant.

Our results showed the 2 main arterial supplies to the foot to be the dorsalis pedis artery and the posterior tibial artery. However, in about 35 percent of the cases there seemed to be contributions from additional vessels, probably the peroneal artery and the malleolar network. According to the detailed anatomical study made by Huber,[8] a branch of the anterior tibial artery about 5 cm above the ankle joint is present as a vessel of significant size about half the time. This vessel anastamoses with the peroneal artery. Huber made no mention of a sex-related difference in occurrence of this vessel, and we cannot explain the difference in collateral arterial supply to the great toe seen in our study.

There seemed to be no difference in the frequency with which the dorsalis pedis artery and the posterior tibial artery sup-

plied the great toe in the present study. The numbers of feet showing a decrease of the blood pressure only after compression of the dorsalis pedis artery or the posterior tibial artery (65 and 47 feet respectively) were not statistically different. In the 34 feet where blood pressure decreased after compression of the dorsalis pedis artery *and* after compression of the posterior tibial artery, no statistically significant difference between the magnitude of decreases could be demonstrated.

In half the cases in the present study, compression of the dorsalis pedis artery was followed by a decrease of the blood pressure in the great toe. Because of differences in technic and in age distribution of the subjects, our data are not comparable to the results of Spoerel et al,[1] who found that the main blood supply to the toes came from the dorsalis pedis artery in 16 percent of the cases.

The reduction in blood pressure following compression of the dorsalis pedis artery never exceeded 44 percent of the blood pressure prior to compression. However, in 4 cases compression lowered the pressure in the great toe below 40 mm Hg, a level believed to be associated with clinical symptoms of inadequate blood supply.[10] Thus, although the dorsalis pedis artery contributed significantly to the blood supply of the great toe in half our cases, clinically important reduction in pressure following occlusion of the artery was observed in only 2 percent of the cases. Measurement of blood pressure in the great toe was more reliable than judging collateral circulation by observation of capillary refilling time, especially when the feet were cold.

If the dorsalis pedis artery is to be cannulated for monitoring blood gases and arterial blood pressure, our present findings indicate that in 2 percent of cases the artery will not be palpable and in another 2 percent it will probably be unsafe to cannulate the artery, as the blood pressure in the great toe would decrease to less than 40 mm Hg. In these cases, if the artery should thrombose because of cannulation, the blood supply to the great toe might be permanently jeopardized. In the remaining 96 percent of the cases, the immediate risk of low blood pressure in the great toe following cannulation of the artery seems minimal. However, in two-thirds of the cases only the posterior tibial artery supplies the toes, should the dorsalis pedis artery be occluded. In the last third of the cases, collateral blood supply other than that through the posterior tibial artery will provide a reserve, but the extent of this collateral circulation is difficult to predict unless blood pressure in the toes is measured. It must be remembered that our study consisted of rather young subjects (median age, 28.7 years), whose collateral circulation is optimal.

Because of these findings, because attempts to estimate the adequacy of collateral circulation by observing capillary refilling after blanching the great toe were unreliable, and because in older age arteriosclerosis may further adversely affect collateral circulation, we conclude that the dorsalis pedis artery should not be selected as a routine site for arterial cannulation.

ACKNOWLEDGMENT

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Increasing Halothane Concentrations Reduce Nitroprusside Dose Requirement

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There has been no description of the hemodynamic dose-response relationship between halothane and sodium nitroprusside (SNP), although these drugs are used together frequently for induction of deliberate hypotension. Utilizing aortic root cannulation and thermister-tipped pulmonary artery catheterization, this relationship was studied in 6 beagles receiving a standard 100 μg/kg infusion of SNP solution administered at 3 different infusion rates (5, 10 and 20 μg/kg/min) while anesthetized with 3 different concentrations of halothane (0.5, 1, and 2%). Sodium nitroprusside infusion resulted in dose-related reductions in mean arterial pressure, systemic vascular resistance, and left ventricular stroke work. Increasing concentrations of halothane significantly potentiated the hypotensive effects of SNP. Cardiac output increased as the SNP infusion rate increased, whereas increasing the halothane concentration resulted in a reduction of cardiac output at each SNP infusion rate studied. Pulmonary artery wedge pressure was significantly reduced by SNP infusion at all 3 halothane concentrations, whereas mean pulmonary artery pressure was unchanged. Arterial pH fell in response to each SNP infusion, from 7.46 at the beginning of the study to 7.32 at the end ($p<0.001$). Sodium nitroprusside predictably induced hypotension during halothane anesthesia at the cost of a dose-related metabolic acidosis. Increasing the depth of halothane anesthesia afforded a greater percentage reduction in arterial pressure at each SNP infusion rate studied. Metabolic acidosis, however, developed no more rapidly at 2% halothane than it did at 0.5 or 1%.

Key Words—ANESTHETIC TECHNICS, induced hypotension, nitroprusside. ANESTHETICS, volatile, halothane.

BOTH halothane and sodium nitroprusside (SNP) are used frequently to induce deliberate hypotension during operative procedures, either individually or in combination. As recently pointed out by Tinker and Michenfelder, "There is a clinical impression that the dosage requirement for nitroprusside is altered inversely by the concentration of volatile anesthetic administered. No studies to document this have been reported."[1] For this reason, a systematic study of the dose-response relationship between SNP and various anesthetics was undertaken utilizing a canine model.

METHODS

Six healthy, fasted, unpremedicated beagles weighing 10 to 15 kg were anesthetized with 1 to 2% inspired halothane in O_2. Following endotracheal intubation, the dogs were placed in left lateral decubitus position, and mechanical ventilation was instituted with a tidal volume of 15 cc/kg, maintaining $Paco_2$ at 33.6 torr ± 0.6 (mean ± SD). An IV infusion of 0.9% NaCl solution was begun in the foreleg and a 16-gauge cannula was passed to the aortic root via a carotid artery cut-down. A 5-French pediatric quadruple-lumen thermodilution cath-

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eter* was placed in an external jugular vein and passed into the right or left pulmonary artery (PA) under manometric control. The PA temperature was maintained at 38.0 ± 0.1 C by external warming, and a 0.1% succinylcholine solution was infused at a constant rate throughout the study to prevent muscular activity.

Mean aortic, pulmonary artery, pulmonary capillary wedge, and right atrial pressures were measured utilizing Statham P50 transducers and recorded with a Grass polygraph. Cardiac output was estimated by thermodilution technic using a 3-ml bolus injection of dextrose 5% in water (D_5W) at room temperature and a KMA Model 3500 computer.* This technic had been calibrated previously to ±10% utilizing both dye-dilution and Fick-principle measurements. All hemodynamic measurements were performed in triplicate during 10 seconds of apnea at functional residual capacity. Blood samples were drawn at the beginning and end of the study for the determination of plasma cyanide and thiocyanate levels.[2]

The protocol called for each dog to receive SNP at 3 infusion rates (5, 10, and 20 μg/kg/min) during anesthesia at 3 different end-tidal concentrations of halothane (0.5, 1, and 2% [Beckman LB-1 analyzer]). The sequence of halothane administration and of SNP infusion was random. After an hour of equilibration at each halothane concentration, control hemodynamic and arterial blood-gas measurements were performed. Sodium nitroprusside solution was prepared by diluting 2 mg of SNP/kg body weight in 1000 ml of D_5W. This solution was infused in 50-ml aliquots (each containing 100 μg/kg of SNP) via a foreleg vein using an infusion pump set to deliver either 2.5, 5, or 10 ml/min in random sequence. The times for infusion at 5, 10, and 20 μg/kg/min were thus 20, 10, and 5 minutes respectively. Arterial pressure fell to a stable level within 1 to 2 minutes after beginning SNP and remained reasonably constant throughout the infusion. Hemodynamic and arterial blood-gas measurements were performed during the last minute of each SNP infusion. Arterial pressure and heart rate then were allowed to return to control levels over the ensuing 5 to 10 minutes before the next SNP infusion was begun.

Hemodynamic parameters were averaged and derived parameters were computed from the following formulas:

(1) Systemic vascular resistance (dyn sec cm^{-5}) = $\frac{\text{mean arterial pressure} - \text{mean right atrial pressure}}{\text{cardiac output}} \times 0.79$

(2) Stroke volume (ml) = $\frac{\text{cardiac output}}{\text{heart rate}}$

(3) Left ventricular stroke work (joule × 10^{-3}) = mean arterial pressure × stroke volume × 0.133

The data were analyzed in 2 ways: first, by comparing SNP-infusion data to the corresponding control values obtained at the same concentration of halothane using Student's *t*-test for paired data; and secondly, by comparing the data observed at 0.5, 1, and 2% halothane during the same infusion rate of SNP using analysis of variance and critical difference testing. Values of p less than 0.05 were regarded as significant.

RESULTS

Sodium nitroprusside infusion during halothane anesthesia resulted in significant dose-dependent reductions in mean arterial pressure (MAP) (fig 1). At each infusion rate of SNP studied, doubling the halothane concentration resulted in a significant reduction in MAP. Systemic vascular resistance was likewise reduced in dose-dependent fashion by SNP infusion (fig 2). Although halothane had minimal effect on SVR dur-

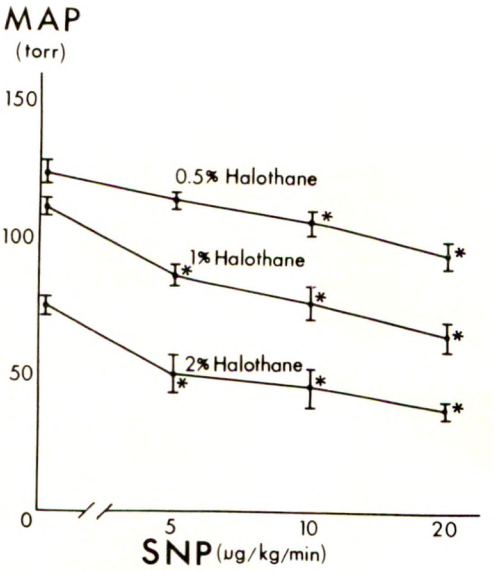


FIG 1. Relationship of MAP to SNP infusion rate during halothane anesthesia. Increasing the concentration of halothane resulted in significant ($p<0.05$) reductions in MAP for each infusion rate of SNP studied. Vertical bars indicate ± SEM. Asterisks indicate significant changes from control ($p<0.05$).

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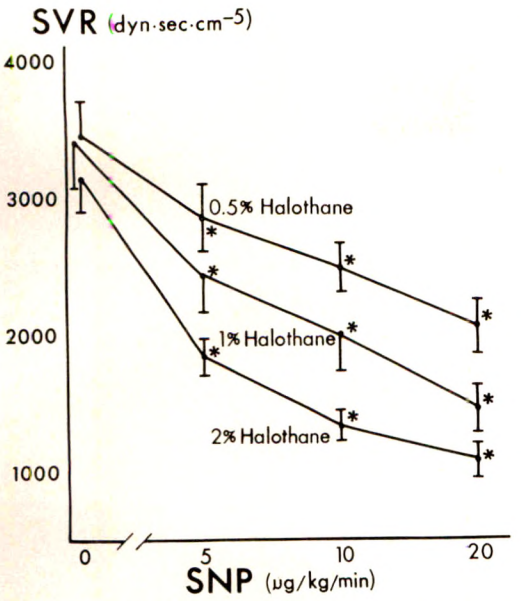


FIG 2. Relationship of systemic vascular resistance to SNP infusion rate during halothane anesthesia. Values obtained at 2% halothane were significantly ($p<0.05$) lower than those observed during 0.5% halothane at the same infusion rate of SNP. Infusion of SNP resulted in significant ($p<0.05$) reductions in SVR at each concentration of halothane.

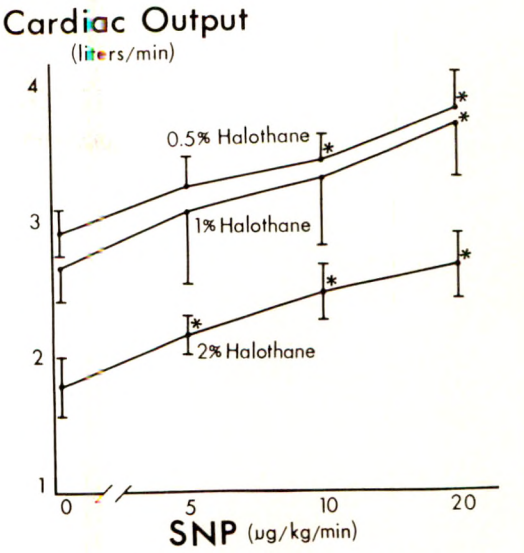


FIG 3. Cardiac output was increased significantly by progressively greater SNP infusion rates at all concentrations of halothane. At each infusion rate of SNP studied, however, cardiac output was always significantly lower at 2% halothane than at either 0.5 or 1%.

ing control measurements, increasing concentrations of halothane caused dose-dependent reductions in SVR at all 3 SNP infusion rates, though the changes were only significant between the 0.5 and 2% concentrations. Cardiac output was increased by SNP infusion in a dose-related fashion (fig 3). At each SNP infusion rate studied, however, cardiac output was significantly lower during 2% halothane than it was during either 0.5 or 1% halothane.

The table summarizes the remainder of the measured and/or calculated hemodynamic parameters. Heart rate rose significantly with SNP infusion at 0.5 and 1% halothane, but was unchanged at 2% halothane. Stroke volume was unaffected by SNP infusion at 0.5 and 1% halothane, but rose significantly with increasing SNP infusion rates at 2% halothane. Mean right atrial and pulmonary artery pressures were not changed, either by increasing the SNP infusion rate or by altering the halothane concentration. Pulmonary vascular resistance tended to fall during SNP infusion, concomitant with the rise in cardiac output. Pulmonary artery wedge pressure, however, was significantly reduced by SNP infusion at all 3 halothane concentrations, as was left ventricular stroke work.

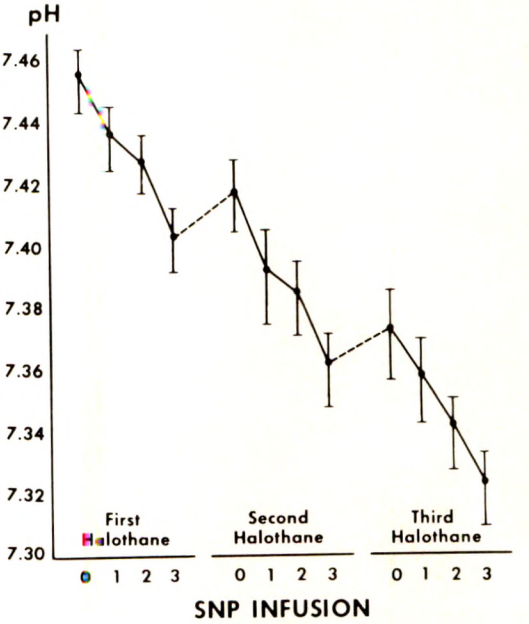


FIG 4. Mean arterial pH plotted sequentially, with P_{CO_2} remaining constant (33.6 torr ± 0.6 SD) throughout the study. (Halothane and SNP dosages both were administered in random order.) Each 100 µg/kg SNP infusion caused a stepwise fall in pH from control values (zero SNP) irrespective of the halothane concentration or the rate at which SNP was infused. The pH tended to recover during the 1-hour equilibration period between different halothane concentrations, but fell further as soon as SNP infusion was reinstituted.

TABLE

Hemodynamic Response to Nitroprusside Infusion at Three Concentrations of Halothane (Mean ± SE)

Halothane concentration	0.5%				1.0%				2.0%			
SNP infusion rate (μg/kg/min)	0	5	10	20	0	5	10	20	0	5	10	20
Heart rate (beats/min)	105	129*	141*	156	106	144*	155*	150*	111	120	119	125
	±8	±5	±6	±9	±5	±11	±13	±15	±5	±8	±5	±7
Stroke volume (cc)	28	25	25	25	25	21	21	24	16	18*	20*	21*
	±2	±2	±2	±2	±3	±3	±2	±3	±1	±1	±1	±2
Mean right atrial pressure (torr)	3	2	2	2	3	2	2	2	5	4	5	4
	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1	±1
Mean pulmonary artery pressure (torr)	16	14	15	15	14	13	14	14	13	13	13	12
	±1	±1	±1	±1	±1	±1	±1	±1	±1	±0.4	±0.4	±1
Pulmonary wedge pressure (torr)	7.6	5.8*	5.5*	6.2*	6.8	5.3*	5.3*	5.4*	8.0	6.2*	6.3*	6.5
	±0.4	±0.6	±0.6	±0.5	±0.6	±0.7	±0.8	±0.6	±1.0	±0.8	±0.7	±0.9
Pulmonary vascular resistance (dyn sec cm^{-5})	277	197	213	199	234	228	222	193*	236	246	210	184
	±28	±21	±21	±28	±25	±25	±29	±13	±38	±24	±33	±26
Left ventricular stroke work (joule × 10^{-3})	459	382*	342*	308*	374	246*	220*	206.7*	175	127*	125*	106*
	±39	±31	±23	±30	±42	±41	±29	±26	±24	±17	±15	±12

*$p<0.05$ vs control values at the same halothane concentration

Anesth Analg 57:457-462, 1978

Blood-gas analysis showed no significant change in either Pao_2 or $Paco_2$ during SNP infusion at any of the halothane concentrations administered. The pH, however, was found to fall progressively in response to each 100 μg/kg SNP infusion, but then tended to recover during the 1-hour equilibration period between changes in halothane concentration (fig 4). The pH fell no more rapidly at 2% halothane, however, than it did during 0.5 or 1% halothane.

Plasma cyanide levels drawn at the beginning and end of each study rose from 1.4 μg/100 ml ± 0.5 SE to 4.5 μg/100 ml ± 0.6 SE ($p<0.05$). Plasma thiocyanate remained unchanged during the study at 0.7 mg/100 mg ± 0.1 SE.

DISCUSSION

To our knowledge, this is the first study specifically designed to examine the hemodynamic dose-response interaction between SNP and several concentrations of a volatile anesthetic. The dose-dependent reduction in MAP seen with increasing concentrations of halothane during SNP infusion indicates that a considerable saving in total SNP dose can be realized clinically by increasing the depth of anesthesia, albeit at the cost of a reduction in cardiac output. By converting our arterial pressure data to percentage change from control values, we observed that each time the concentration of halothane was doubled, there was a greater fall in pressure from control values during all 3 rates of SNP infusion (fig 5). At the 5 μg/kg rate, the degree of hypotension induced by SNP was significantly greater at 1% halothane than it was at 0.5%, and similarly was greater at 2% than at 1%. Thus, at an SNP infusion rate of 5 μg/kg/min, doubling the halothane concentration causes about the same absolute pressure reduction as occurs when the SNP infusion rate is increased to 20 μg/kg/min.

Our data confirm previous studies which demonstrated that the hypotensive effect of SNP is caused primarily by dilation of arterial resistance vessels,[3,4] whereas halothane acts primarily as a depressant of myocardial contractility.[5] The combination of these drugs results in approximately parallel changes in arterial pressure, systemic vascular resistance, and cardiac output as the concentration of halothane is increased. It remains to be elucidated whether increasing concentrations of enflurane might result in progressively steeper reductions in arterial

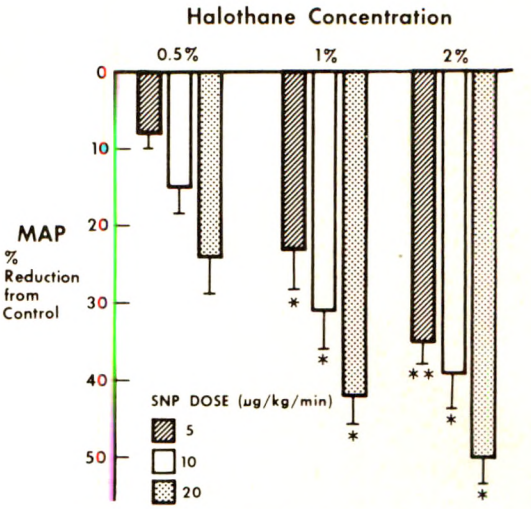


FIG 5. Sodium nitroprusside–induced hypotension data plotted as percent change from control values. As the halothane concentration increased, the same infusion rate of SNP resulted in progressively greater falls in MAP. Single asterisk indicates $p<0.05$ vs 0.5% halothane at the same SNP infusion rate. Double asterisk indicates $p<0.05$ vs 1% halothane at the same SNP infusion rate.

pressure during SNP infusion, since enflurane appears to have a slightly greater effect on peripheral vascular resistance than does halothane.[6]

One of the major potential complications of large-dose SNP administration is metabolic acidosis, which results from the release of cyanide as SNP is metabolized. This has been observed in both humans[7,8] and dogs,[9] often associated with hemodynamic "resistance" to SNP. The toxic threshold for SNP in man has been reported to be as low as 1.5 mg/kg for short-term infusion,[10] whereas signs of toxicity have been seen in dogs receiving doses greater than 1 mg/kg.[9] The progressive acidosis which developed with each 100 μg/kg SNP dose in this study presumably is a result of the toxic effects of cyanide, since pH rose during the 1-hour period between SNP infusions. The total SNP dose of 0.9 mg/kg used in this study is close to the previously reported toxic limit for dogs, and calculated base excess fell by a mean value of 10 mEq/L from the start to the end of the study. Thus, the effects of cyanide toxicity presented not as a threshold phenomenon, but as a continuum of gradually increasing acidosis. Since individual sensitivity to cyanide toxicity may vary widely in clinical practice, documentation of acid-base status even during low-dose SNP therapy appears warranted.

In summary, SNP infusion was found to produce a predictable, dose-related hemodynamic response during halothane anesthesia. The price paid for this effect is the development of an equally dose-dependent metabolic acidosis, which probably reflects cyanide toxicity. Increasing the depth of halothane anesthesia appears on the basis of these animal data to be a safe technic for reducing the total dose of SNP required for the induction of deliberate intraoperative hypotension.

ACKNOWLEDGMENT

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REACTIONS TO INTRAVENOUS INDUCTION AGENTS

Adverse reactions to IV anesthetic induction agents in an estimated 108,708 cases were surveyed retrospectively in a large anesthetic department. Agents and their estimated incidence of use were thiopental (79.6%), Althesin (17.1%), methohexital (2.3%), and propranidid (1.0%). In 4 years, 26 reactions were recorded, 20 associated with Althesin and 6 with thiopental. Half the reactions showed features of histamine release and were sufficiently severe in 5 patients to cause cardiac arrest. Apart from 6 miscellaneous reactions, equally divided between the 2 drugs, 7 neuromuscular reactions, 4 generalized convulsions, and 3 cases of severe muscle rigidity occurred after Althesin. The overall incidence of adverse reactions was 1:900 after Althesin and 1:14,000 after thiopental. *(Evans JM, Keogh JAM: Adverse reactions to intravenous anaesthetic induction agents. Br Med J 2:735-736, 1977)*

Evaluation of the Swank IL-201 Transfusion Filter

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The effects of a new transfusion filter (Swank IL-201) on stored, whole blood have been examined. Six filters were preloaded by passage of two units of outdated, type-specific bank blood, and the effects of filtration on a third unit of 21-day-old blood flowing under 150 mm Hg pressure were measured. Filtration did not significantly alter erythrocyte or leukocyte count, total or plasma hemoglobin, red-cell fragility, and plasma sodium, potassium, albumin, or globulin. Platelet counts were reduced by 33%. Removal of microaggregates, assessed by Coulter counting, screen filtration pressure, total screen protein, wet and dry weight of material retained, and scanning electron microscopy, was shown to be effective over the entire range of particle size.

In comparison with other transfusion filters previously examined in this laboratory, the Swank IL-201 filter combines the features of efficient microaggregate removal with moderate blood-flow rate. Compared to its predecessor, the Swank IL-200, this new filter design has improved flow characteristics without loss of microaggregate removal efficiency.

In view of the similarity of performance demonstrated for several of the available filters, it seems likely that relative cost will constitute an important determinant of filter selection.

Key Words — TRANSFUSION, filters. BLOOD, filters. EQUIPMENT, transfusion filters.

MICROAGGREGATES of platelets, cell debris, and fibrin form during storage of whole blood.[1-3] It has been suggested that respiratory insufficiency following massive blood transfusion is due, in part, to pulmonary vascular obstruction by resulting microembolization of pulmonary arterioles and capillaries.[4] Transfusion filters were introduced to remove microaggregates prior to infusion of stored blood. There are currently five such filters commercially available.

The purpose of the present study was to evaluate a new transfusion filter, Swank IL-201 (Extracorporeal Medical Specialties, Inc.), in a study design previously employed in this laboratory.[5-8] The performance of the Swank IL-201 was compared with that of

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its predecessor, Swank IL-200, as well as with the four other presently available filters, namely Bentley PFF-100, Fenwal 4C2423 (Fenwal 20 Micron High-Capacity Transfusion Filter), Johnson & Johnson Company Intersept,® and Pall Corporation Ultipor® filters.

STUDY DESIGNS

Study A—Six Swank IL-201 filters were studied, and for each filter the following protocol was followed: two units of type specific, outdated (21 to 26 days old) blood were run through the filter, followed by a third test unit of blood that had been stored for 21 days. The flow of blood for all three units was assisted by a constant 150-torr applied pressure. After passage across the filter the blood from the test unit was collected in a Fenwal Transfer Pack.

Samples of blood from the test unit were analyzed for screen filtration pressure; microaggregate count; volume and size distribution; platelet, erythrocyte, and leukocyte count; packed cell volume; plasma hemoglobin; proteins (total and fractional); serum sodium and potassium; and erythrocyte fragility. Measurements were performed on the fresh blood and then after 21 days of storage, before and after filtration. The blood samples were collected in plastic syringes with a Swinnex filter holder containing a woven nylon screen with 170-μm diameter holes. This material was identical to that used for the clot filter incorporated in the clinical transfusion sets, and thus the samples obtained were representative of the blood that would be transfused into a patient.

In addition, rates of blood flow across the Swank IL-201 filters were measured and the wet and dry weights of material removed were evaluated. The material collected on the 170-μm clot filters and on the screens used to measure screen filtration pressure was examined by scanning electron microscopy.

Study B—An additional six filters were examined for evidence of contamination of the effluent with foreign material incorporated during the manufacturing process.

For each filter, 450 ml of normal saline were connected to a 0.45-μm Millex® filter (Millipore Corp.) and appropriate plastic tubing. An initial 50 ml of saline were allowed to flow through the system to flush it and were then discarded. A Swank IL-201 filter was then interposed distal to the Millex filter, and below that a nickel screen filter with 20-μm diameter holes was inserted in a Plexiglas holder. Saline was allowed to flow across the apparatus until 20 ml had emerged; the flow was then interrupted, and the screen filter A removed and replaced with a fresh one (B). An additional 180 ml of saline were allowed to flow; the screen filter was changed again (C), and the final 200 ml of saline run through. In all cases the saline flowed by gravity without the application of external pressure.

Each of the three screens (A, B, and C) was dried in a dust-free atmosphere and examined microscopically. The number and character of collected material were noted for each. Five additional complete runs were made as previously described except that a Swank IL-201 filter was not interposed. The number and character of material collected on these screens served as controls for the procedure.

ANALYTIC METHODS

The test units of blood utilized in Study A were obtained from paid, male, adult, human volunteers after the nature of the study had been explained and a written consent signed. These subjects were asked to refrain from taking any drugs for 1 week and from smoking for 24 hours before reporting to the donor station.

Blood was collected in plastic bags (Fenwal Blood-Pack) to a final concentration of 450 ml of blood in 63 ml of citrate-phosphate-dextrose (CPD) anticoagulant. The bags were mixed at least five times during the collection and were then stored for 21 days at 4 C in a blood refrigerator.

Screen Filtration Pressure (SFP) — A modification of the method of Swank[9] was employed for the measurement of SFP.[7] A Plexiglas container holding a nickel screen with pores 20 μm in diameter was filled with physiologic saline solution and connected to a syringe containing 3 ml of blood. The syringe was placed in a high-pressure Harvard pump which, when activated, forced blood across the screen at a constant rate of 2 ml/10 sec. A calibrated transducer and Texas writer recorded the pressure generated immediately proximal to the screen. The final pressure reached after 10 seconds of blood flow minus the pressure observed with saline solution was the SFP. The final value for each blood sample was obtained from the mean of triplicate determinations.

Total Screen Protein—Two screens from each of the above measurements of SFP were washed with 100 ml physiologic saline solution and then placed separately in 2 ml warm 1 N sodium hydroxide. The protein content in the final solution was measured spectrophotometrically.[10]

Microaggregate Counts — The number, size, and volume distribution of microaggregates contained in the blood were measured with a Coulter Model TA Counter.[11]

Fifty microlitres of blood were added to 10 ml of Isoton (Coulter Diagnostics, Inc.) containing 5 1 25% Zap-o-globin solution. Particle analysis was begun after 15 seconds and completed 15 seconds later; the diluted suspension was stirred throughout. Each final microaggregate analysis, covering 9 channels from 12.7 to 80.6 m in diameter, was obtained as the mean of 5 separate determinations. The results are presented as numbers and volumes of particles in each size range and their totals.

Cell Counts — Platelet counts were performed in triplicate by phase microscopy, according to the method of Brecher et al.[12] Erythrocyte count, leukocyte count, packed cell volume, and total hemoglobin determinations were performed in duplicate by standard technics with a Model S Coulter Counter. Specific gravity of blood was measured by weighing a precise volume of blood.

Plasma Electrolytes, Hemoglobin, and Proteins—Plasma was obtained by centrifugation of whole blood at 3000 rpm for 10 minutes at 4 C. The supernatant was stored frozen at −4 C until it was analyzed. Plasma sodium and potassium were measured with a flame photometer (Instrumentation Laboratories Model #343). Plasma hemoglobin was determined by spectrophotometry, utilizing the method of Lindberg et al.[13] Plasma proteins were measured and fractions quantified by electrophoresis (Helena System).

Erythrocyte Fragility—Fragility of erythrocytes was tested with a Fragilograph (Elron Electronics Industries Model D-2) by measuring the concentrations of saline solution when hemolysis began and was completed.

Blood Flow Rate—For each test unit, the time required for the blood to flow across the filter was measured with a stopwatch. The blood volume was obtained from the weight of each unit, before and after emptying, and from the specific gravity. The rate of blood flow was calculated for each unit from these volumes and times.

Wet and Dry Filter Weights—The micropore filters were dried to a constant weight by aspirating warm, dust-free air. After the first 2 units of outdated blood had run through the filter, 100 ml of air were injected to remove excess blood, and the filter weighed. These 2 measurements provided control wet and dry weights. When filtration of the test unit was completed, 100 ml of air were injected to clear the excess blood and the final wet weight was obtained. The filter was flushed with 1 L of saline solution to wash the blood from the inside casing, and dried in an oven at 60 C until a constant weight was obtained on 2 consecutive days.

The differences between the initial and final wet and dry weights were divided by the volume of filtered blood; this calculation was used to obtain measurements of the wet and dry material retained by the filters per 100 ml filtered blood. The volume of filtered blood was calculated from the weight of the storage bag, full and empty, and the specific gravity of the blood.

Scanning Electron Microscopy—For each blood sample, following measurement of SFP, one of the nickel screens was flushed with 100 ml of saline solution to remove erythrocytes and then fixed in 1% glutaraldehyde. The screen was subsequently dehydrated in graded alcohols and amyl acetate and finally subjected to critical-point drying. Molecular layers of carbon and gold were deposited on the surface, and the specimen was examined in a JEOL JSM50-A scanning electron microscope. Photomicrographs at 60 and 1800 × magnification were obtained. In addition, samples from the various components of the micropore filter were treated similarly, examined, and photographed. The data obtained from these measurements were analyzed for statistical significance by Student's *t*-test.

RESULTS

Study A—The means and standard errors of the data are shown in tables 1 and 2. In both tables, the data obtained on day 0 confirm that the blood was normal at the time of collection, both with respect to the plasma and cellular components and in having minimal microaggregates, as indicated by the small values for screen filtration pressure and total screen protein. Some of the

TABLE 1
Study A: Plasma Component in Test Units
(Mean ± Standard Error)

	Day 0	Day 21	
		Prefiltration	Postfiltration
Plasma hemoglobin (mg/100 ml)	...	37.1 ±6	36.3 ±4
Plasma sodium (mEq/L)	172 ±4	160 ±5	162 ±5
Plasma potassium (mEq/L)	3.5 ±0.1	22.9 ±1.2	23.5 ±0.5
Albumin (g/100 ml)	3.76 ±0.07	3.73 ±0.08	3.73 ±0.05
Globulin (g/100 ml)	2.14 ±0.10	2.25 ±0.10	2.34 ±0.10
Fibrinogen (mg/100 ml)	217 ±17	227 ±32	227 ±35

well-known changes associated with storage of blood are also demonstrated in comparing the data from day 0 to those of day 21 prefiltration.

The results of plasma analysis before and after filtration are shown in table 1. There were no significant changes in plasma hemoglobin, sodium, potassium, albumin, globulin, or fibrinogen. Table 2 shows that filtration was not associated with loss of erythrocytes or white blood cells, or with changes in total hemoglobin, packed cell volume, or erythrocyte fragility; however, a significant ($p<0.05$) reduction of platelet count was observed. The formation of microaggregates in the blood during storage for 21 days is documented in table 2 by the substantial increase in SFP, total screen protein, and microaggregate volume observed. All of these changes were significantly ($p<0.05$) reduced by filtration.

A detailed analysis of the effect of filtration on microaggregates over the 9 channel diameters examined, from 12.7 to 80.6 μm, is shown in fig 1. The filter removed particles over the whole range of sizes. The total number of microaggregates present was a mean of 434/mm^3 before and 217/mm^3 after filtration.

The wet weight of material retained by the filter with passage of the test unit was a mean of 670 mg/100 ml, and the dry

TABLE 2
Study A: Microaggregates and Blood Cell Components of Test Units
(Mean ± Standard Error)

	Day 0	Day 21	
		Prefiltration	Postfiltration
Screen filtration pressure (mm Hg)	13 ±1	249 ±39	15* ±2
Total screen protein (μg/screen)	45 ±16	205 ±33	64* ±7
Microaggregate volume (x $10^3 \mu m^3/mm^3$)		335 ±31	52* ±10
Erythrocyte count (x $10^6/mm^3$)	4.57 ±0.14	4.54 ±0.12	4.55 ±0.12
Platelet count (x $10^3/mm^3$)	143 ±7	52 ±6	35* ±4
Leukocyte count (x $10^3/mm^3$)	4.4 ±3	2.9 ±0.1	2.6 ±0.1
Erythrocyte fragility			
NaCl% Onset	0.53 ±0.03	0.54 ±0.02	0.53 ±0.02
NaCl% Complete	0.24 ±0.02	0.20 ±0.01	0.22 ±0.01
Packed cell volume (%)	40.9 ±1.0	42.1 ±0.9	42.0 ±0.8
Total hemoglobin (g/100 ml)	13.3 ±0.3	13.2 ±0.3	13.1 ±0.3

*Indicates postfiltration value significantly different from prefiltration value ($p<0.05$)

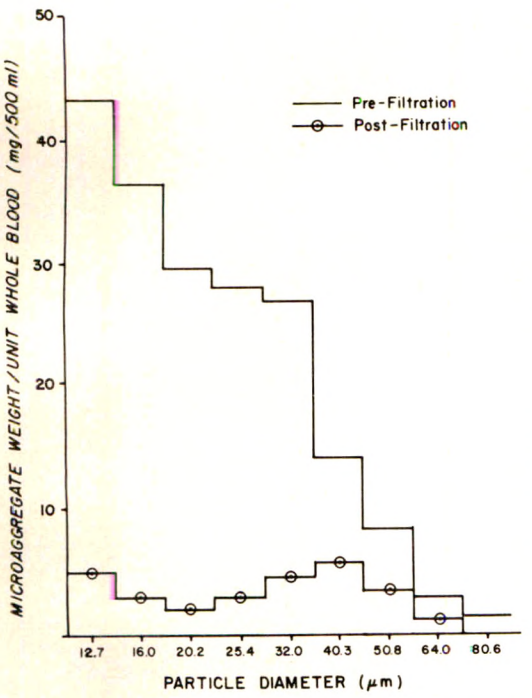


FIG 1. Coulter analysis of mean microaggregate weight in each channel diameter before and after filtration with Swank IL-201 filter. Substantial microaggregate removal at all diameters is evident. The Coulter data for each channel were multiplied by 5.45×10^{-4} to convert from volume ($\mu m^3/mm^3$) to weight (mg/500 ml) of microaggregate (assuming a specific gravity of 1.09).

weight of retained material calculated from all 3 units was a mean of 175 mg/100 ml.

Scanning electron photomicrographs of the SFP screen (fig 2) show the considerable quantity of material observed before, and the reduction following, filtration.

Study B—The only foreign material observed on the screens were small, irregular strands (probably cellulose dust). The total number of these fibers observed on all screens (A, B, and C) with all 6 filters was 3 (1 fiber was demonstrated from each of 3 filters only). However, the total number of similar fibers observed with the controls was also 3. It was, therefore, concluded that no contamination of the effluent could be attributed to the filter.

DISCUSSION

The performance of the Swank IL-201 with respect to normal plasma and blood-cell components was similar to that of other transfusion filters examined previously. No significant effects were detected on erythrocyte or leukocyte count, total or plasma hemoglobin, packed cell volume, or red-cell fragility, and thus damage to, or removal of, erythrocytes did not occur. For some of the depth filters previously examined in this laboratory, an increase of plasma hemoglobin was measured after filtration; this was not observed following filtration with this filter, although it should be emphasized that the degree of hemolysis observed with other filters was small and of no apparent clinical significance.

As with all the other filters, the use of the Swank IL-201 did not result in changes in the plasma albumin, globulin, fibrinogen, sodium, or potassium. A significant decrease in platelets occurred, and it was shown in a previous study that this change is a result of the presence of the filter, and not the transfer to the Fenwal Transfer Pack. Assuming that the latter changes also occur with viable platelets and leukocytes, the use of the filters is not advised when specific replacement of these components is desired.

In table 3, some principal characteristics of the two Swank filters are compared. It is apparent that the new design of the IL-201 has resulted in a significant increase in blood-flow rate without loss of efficiency in removing microaggregate material. Compared with the IL-200 filter which was previously examined in our laboratory, the packing density of the media was decreased and the fiber diameter increased. Figure 3 compares the Swank IL-201 filter with the other presently available filters that have been examined in this laboratory in identical study designs. Efficiency of microaggregate removal, as judged by wet weight of retained material, change of SFP, or change

TABLE 3
Comparison of Swank IL-200 and IL-201 Filters
(Mean ± Standard Error)

	Swank IL-200	Swank IL-201
Blood flow rate (ml/sec)	2.5 ±0.6	4.75* ±0.5
Change of screen filtration (pressure %)	94 ±3	99 ±1
Change of microaggregate volume (%)	75 ±7	76 ±6

*Indicates value for IL-201 significantly different ($p<0.05$) from IL-200 by unpaired Student's t-test

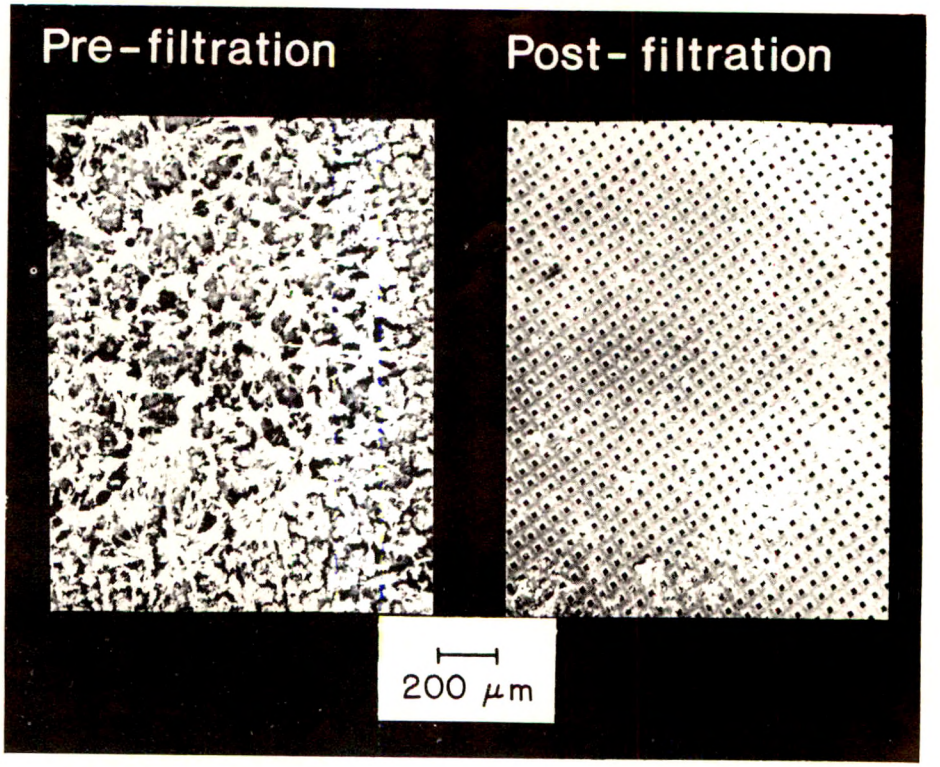


FIG 2. Scanning electron photomicrograph of the SFP screen before and after filtration with Swank IL-201. Removal of much of the microaggregate material is indicated.

in microaggregate volume, shows the Swank IL-201 to be comparable with the most efficient filters. The greater the weight of material removed, the reduction (ie, percent change) in microaggregate volume, and the reduction of SFP, the better the filter is meeting its purported purpose, the removal of microaggregates. Blood-flow time for the Swank IL-201 was significantly greater (ie, allowed a slower flow rate) than for some of the other filters, but the difference is unlikely to be of clinical importance.

The absence of foreign material (ie, fibers) on the SFP screen in Study A and the finding, in Study B, that no contamination of the effluent could be attributed to the Swank IL-201 filter make this an unusually "clean" filter.

In summary, the Swank IL-201 filter combines the features of efficient microaggregate removal with a moderately rapid flow rate.

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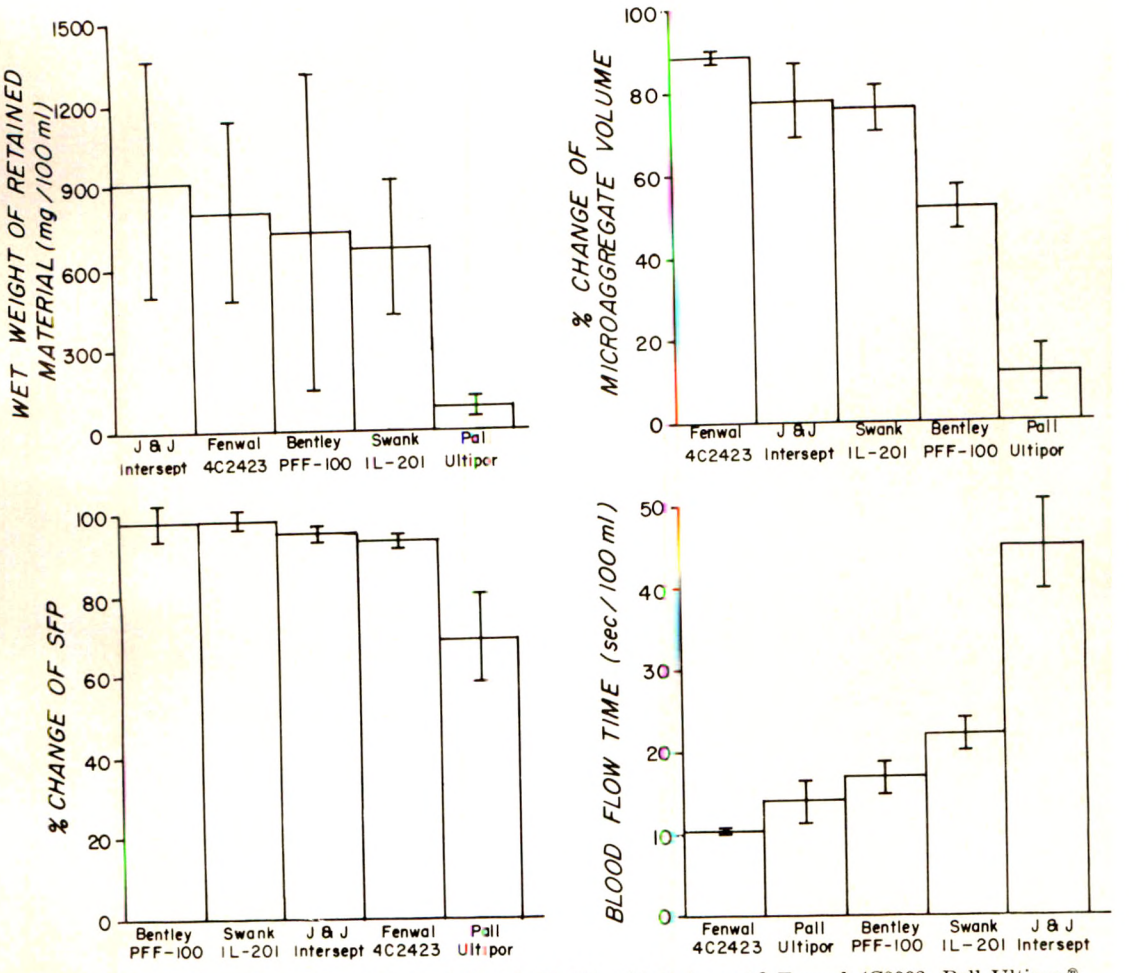


FIG 3. Comparison of principal effects of Swank IL-201 with Intersept,® Fenwal 4C9003, Pall Ultipor,® and Bentley PFF-100 on microaggregates and blood-flow rate. Mean ± standard errors are shown. The ordinates (percent change of SFP and microaggregate volume) are calculated from: (values before filtration – value after filtration) ÷ (value before filtration) × 100.

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Low-Frequency Positive Pressure Ventilation with Extracorporeal Carbon Dioxide Removal (LFPPV-ECCO$_2$R): An Experimental Study

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We describe a new form of mechanical pulmonary ventilation, low-frequency positive pressure ventilation with extracorporeal CO_2 removal (LFPPV-ECCO$_2$R). In a series of animal studies the rate of mechanical ventilation was 0.66, 1, 2, and 4 min^{-1} at a tidal volume of 3, 10, and 15 ml kg^{-1}. We were able to maintain normal blood gases and normal lung volumes and lung mechanics even at the lowest ventilator rate with tidal volumes of 10 or 15 ml kg^{-1}. Each experiment lasted 7 hours. Our data suggest a possible new dimension in the management of a difficult patient on mechanical pulmonary ventilation.

Key Words—VENTILATION, extracorporeal CO_2 removal and.

SINCE the introduction of intermittent positive pressure breathing (IPPB) in respiratory treatment some twenty years ago, many forms of mechanical ventilation (MV) have been described: continuous positive pressure breathing (CPPB),[1] high-frequency positive pressure ventilation (LFPPV),[2] and intermittent mandatory ventilation (IMV).[3]

Mechanical ventilation is frequently a life-saving procedure. But depending on the underlying pulmonary disease, 35%,[4] 50%,[5] or 95%[6] of patients treated with MV ultimately die, either of the underlying disease process or of complications of pulmonary therapy with MV. There is a question as to whether MV offers the proper environment for the healing of the lungs, and whether

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it may contribute to the ultimate demise of the patient, since both pulmonary[7,8] and systemic[9,10] complications have been attributed to positive pressure breathing.

The ultimate goal of MV is not merely to prolong life, but to provide an optimum environment for healing of the lungs. Unfortunately, it is not easy to show what constitutes an optimum environment. In pneumonia involving a single lobe, consolidation of the involved lobe with no ventilation is considered the optimal milieu for lung healing. It is not known what constitutes the optimum milieu for lung healing when the lungs are diffusely diseased.

Recently, IMV has been used not only in weaning of the patient from a ventilator, but also in treatment of acute respiratory failure.[11] It has been suggested that mechanical ventilation at a rate of 1 to 2/min coupled with spontaneous breathing results in less barotrauma[12] and has less effect on circulatory hemodynamics.[13] This low rate of mechanical ventilation is not possible when CO_2 elimination by spontaneous respiration is impaired. Whether IMV at this low rate provides a better environment for lung healing remains unproven.

It has been recently shown that spontaneous ventilation for CO_2 removal can be substantially decreased or can stop completely if part or all of the metabolic CO_2 produced is removed by an artificial lung.[14] This suggests the possibility of controlling all forms of MV at will and still maintaining adequate alveolar ventilation. In this report we describe a new form of mechanical ventilation, low-frequency positive pressure ventilation with extracorporeal CO_2 removal (LFPPV-ECCO$_2$R). The total respiratory rate in these experiments was as low as 1 breath every 90 seconds. In studies in healthy paralyzed animals, LFPPV-ECCO$_2$R maintains normal lung volumes, normal lung mechanics, and normal blood gases.

MATERIALS AND METHODS

Five tracheostomized lambs weighing between 12 and 16 kg were anesthetized with pentobarbital, paralyzed with d-tubocurarine, and mechanically ventilated with a Harvard ventilator. The ventilator was modified to give a constant inspiratory-expiratory time ratio of 1:1.5. A small Teflon® catheter (ID 1 mm) was placed through the tracheostomy tube, advanced to the level of the carina, and then connected to a source of O_2. Intratracheal pressures were recorded by a Statham pressure transducer. Total ventilation was continuously monitored with a recording bell spirometer. Positive end-expiratory pressure (PEEP), when used, was obtained by placing an appropriate weight on the top of the bell. Mixed expired gases, partial pressures were measured by a Medical Mass Spectrometer.* Pulmonary gas was aspirated at the end of each study period (ie, every 30 minutes) at a constant rate of 3 ml · sec^{-1} for 20 seconds, and the composition of the gas as it emerged from the tracheal inlet was measured by a Medical Mass Spectrometer. The sampled gases were assumed to be "alveolar" when the P_{CO_2} plateau equaled arterial P_{CO_2} ($\pm$1.5 torr). The functional residual capacity (FRC) was measured by the helium dilution technic and expressed at BTPS. The total static compliance was computed from the tracheal pressure reading after 100 ml of air were injected. Both FRC and total lung compliance were measured at atmospheric pressure. Lycra® polyurethane catheters (ID 3.5 mm) were placed in the subclavian artery and in the external jugular vein, and blood was pumped from the artery through an extracorporeal carbon dioxide membrane lung (CDML), surface area 1.6 m^2, and into the vein. The CDML was designed for optimum CO_2 removal.[15]

The extracorporeal circuit was primed with heparinized lactated Ringer's solution (8 units/ml). Extracorporeal blood flow ranged between 500 and 800 ml min^{-1}. Continuous heparinization was maintained at 100μ kg^{-1} hr^{-1}. Oxygen saturation of arterial hemoglobin was monitored by an on-line oximeter.[16] The membrane lung was ventilated with humidified room air (37 C) at a flow between 3500 and 4000 ml min^{-1}. The gas compartment of the CDML was kept at 200 to 250 mm Hg below the atmospheric pressure. Total CO_2 removed by the CDML was computed from the gas flow and the CO_2 concentration of effluent gas, measured by an infrared CO_2 analyzer,† and expressed at STPD.

The experimental setup is shown in fig 1. Arterial blood samples were obtained before and after the CDML, and the mixed venous blood samples were obtained through a 5 French Swan-Ganz catheter positioned in

*Medical Mass Spectrometer—MM-8, Scientific Research Instrument Corporation, Baltimore, Maryland

†Beckman, Model 315A

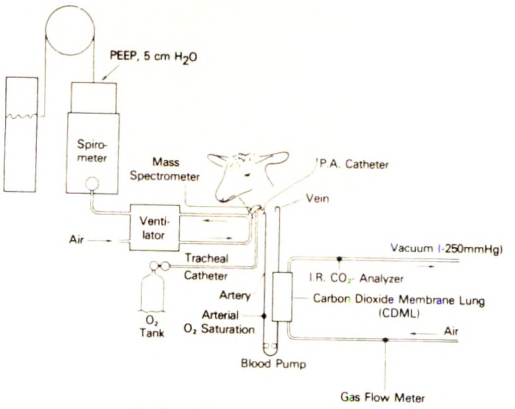


FIG 1. Experimental setup

the pulmonary artery. Blood P_{O_2}, P_{CO_2}, and pH were immediately measured by a Radiometer Blood Gas Analyzer.* Oxygen saturation of hemoglobin was measured by an A.O. Oximeter† calibrated for sheep blood. Total hemoglobin was measured by Drabkin's method. Using standard formulas, from these data we computed O_2 consumption ($\dot{V}O_2$), CO_2 production ($\dot{V}CO_2$), venous admixture fraction (QVA/QT), and cardiac output (CO).

EXPERIMENTAL PROCEDURE

The lambs initially were mechanically ventilated with room air for 30 minutes at 10 ml kg^{-1} tidal volume and at a respiratory rate of 16 min^{-1}. The expiration was passive to the atmosphere (baseline conditions). There was no extracorporeal CO_2 removal at this time (zero gas flow through the CDML). At the end of 30 minutes, a complete set of measurements was taken.

The animals were then started on apneic oxygenation, and CO_2 was removed by the extracorporeal CDML for a period of 30 minutes in the following manner: The mechanical ventilator was stopped and 100% O_2 was supplied to the natural lung through a Teflon® catheter to maintain the lungs inflated at 5 cm H_2O pressure. We then began CO_2 removal by starting the gas flow to the CDML. At the end of 30 minutes a new set of measurements was taken.

Following this, the animals were ventilated at 5 cm H_2O PEEP with room air at 0.66, 1, 2, or 4 breaths min^{-1}. Measurements were taken at tidal volumes (TV) of 3, 10, or 15 ml kg^{-1} at these 4 frequencies after 30 minutes. During all 12 LFPPV periods, the CO_2 was continuously removed by the CDML and 100% O_2 was continuously supplied at 190 ml min^{-1} through the Teflon® cannula. The complete study lasted 7 hours. At the end of the experiments the animals were electively sacrificed.

RESULTS

The CO_2 transfer of the CDML has been previously described, and was consistent with our previous findings.[15] The amount of CO_2 removed was always sufficient to clear the CO_2 production, even during periods of apnea (table 1). The O_2 consumption during the control periods in this series of lambs averaged 5.09 ml kg^{-1} ± 0.59. We did not observe any significant changes in acid-base balance. Table 2 shows the effects of LFPPV-ECCO$_2$R on alveolar gases, arterial and mixed venous blood gases, arterial and mixed venous pH, and arterial and mixed venous blood O_2 content difference. The low-frequency positive pressure ventilation appears to be meaningful from the ventilatory point of view only at TV-15. The P_{aCO_2} at TV-15 is significantly lower than at TV-3 and at TV-10, and decreases with increasing respiratory frequency (fig 2). However, even though without respiratory meaning, different TV ventilation appears to affect lung mechanics and the shunt fraction (table 3). The FRC was a function of the TV and was independent of respiratory frequency (fig 3). Total static compliance correlated with the FRC ($r = 0.96$, $p<0.001$; not shown).

DISCUSSION

These studies were performed at a RR heretofore not possible, and yet we were

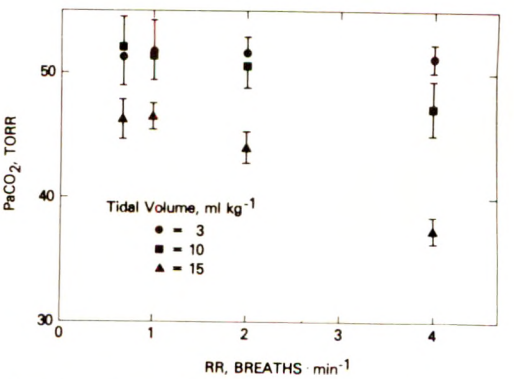


FIG 2. Arterial P_{CO_2} as a function of respiratory rate, at different tidal volumes (mean values ± 1 SE)

*Mod. PHM 27, Copenhagen, Denmark

†A. O. Oximeter, Model 10800, Buffalo, New York

TABLE 1
Performance of the CDML at Different Tidal Volumes and Respiratory Rates
(Mean Values ± 1 SD)

RR breaths · min⁻¹	Apnea 0	TV-3 0.66	TV-3 1	TV-3 2	TV-3 4	TV-10 0.66	TV-10 1	TV-10 2	TV-10 4	TV-15 0.66	TV-15 1	TV-15 2	TV-15 4
P_{CO_2} after CDML (mm Hg)	31.16 ±1.28	32.8 ±3.70	33.1 ±3.36	33.2 ±2.92	32.7 ±2.38	32.1 ±2.19	33.6 ±3.36	30.1 ±3.95	28.4 ±5.40	31.8 ±2.97	34.3 ±5.69	26.6 ±2.88	27.8 ±0.81
		32.9 ± 2.88				31.1 ± 4.68				30.07 ± 4.72			
pH after CDML	7.48 ±0.073	7.486 ±0.088	7.498 ±0.081	7.476 ±0.091	7.476 ±0.083	7.472 ±0.073	7.478 ±0.078	7.496 ±0.077	7.500 ±0.065	7.504 ±0.071	7.524 ±0.085	7.538 ±0.0739	7.520 ±0.063
		7.484 ± 0.079				7.487 ± 0.069				7.522 ± 0.069			
CO_2 transfer (ml min⁻¹)	80.7 ±16	80.14 ±13.84	81.14 ±12.57	82.92 ±17.7	82.90 ±14.9	80.26 ±14.7	80.32 ±14.7	79.24 ±13.2	74.5 ±12.03	76.68 ±13.32	72.14 ±12.11	68.44 ±12.7	63.9 ±13.6
		81.77 ± 13.7				78.58 ± 12.3				70.29 ± 12.7			

FIG 3. Functional residual capacity as a function of tidal volumes, at different respiratory rates (mean values)

able to maintain normal blood gases at RR less than 1/min. The extracorporeal CO_2 removal is the key element; all metabolically produced CO_2 can be removed by the CDML at a relatively low extracorporeal blood flow of 500 to 1000 ml min^{-1}.[15] The technical complexity of extracorporeal CO_2 removal lies between hemodialysis (except that it must be used continuously) and extracorporeal blood gas exchange as used during cardiopulmonary bypass. No doubt LFPPV-ECCO$_2$R can be performed equally well with venovenous or venoarterial pumping.

A second key point is the continuous supply of 100% O_2 delivered directly into the trachea in an amount at least equal to the O_2 consumption. During LFPPV-ECCO$_2$R, the minute ventilation is greatly reduced and results in "alveolar hypoventilation." However, this is a unique form of hypoventilation characterized by a normal PA_{CO_2}. In classical terms hypoventilation implies hypercapnea, but in the LFPPV-ECCO$_2$R the PA_{CO_2} is kept normal as the required amount of CO_2 is removed by the CDML. However, rather than raising F_{IO_2} to prevent alveolar hypoxia, we continuously administered 100% O_2 at 190 ml min^{-1} directly into the trachea at a rate substantially in excess of $\dot{V}O_2$. This insured that the O_2 consumed was continuously replaced, molecule for molecule, and alveolar PA_{O_2} remained unchanged; any excess of O_2 supplied was vented out through the endotracheal tube into the spirometer. It is important that 100% O_2, rather than air, be fed directly into the trachea; as O_2 is consumed, 100% O_2 must be replaced, rather than air which contains mostly nitrogen. By supplying all the O_2 consumed (and remov-

TABLE 2

Alveolar Po_2, Arterial and Mixed Venous Po_2 and Pco_2, and pH: Arterial—Mixed Venous O_2 Differences at Different Respiratory Rates and Tidal Volumes

(Mean Values ± 1 SD)

RR breaths · min^{-1}	Control 16	Apnea 0	TV-3 0.66	TV-3 1	TV-3 2	TV-3 4	TV-10 0.66	TV-10 1	TV-10 2	TV-10 4	TV-15 0.66	TV-15 1	TV-15 2	TV-15 4
PA O_2 torr	98 ±11	135 ±19	247 ±108	232 ±71.8	308 ±102	332 ±70	109 ±19	157 ±45	174 ±35	197 ±40	131 ±40	127 ±28	141 ±35	166 ±38
			286 ± 89				166 ± 57				133 ± 35			
PaO_2 torr	72.6 ±26	63.6 ±7.7	76.6 ±10.2	76.0 ±9.9	74.0 ±9.5	90.2 ±19.6	72.7 ±10.0	78.3 ±4.3	89.4 ±10.6	115.4 ±27.7	70.6 ±12.1	68.7 ±9.12	87.8 ±14.0	99.2 ±30.0
			79.2 ±13.6				90.4 ± 22.8				79.2 ± 13.6			
$PaCO_2$ torr	43.5 ±3.1	50.6 ±6	51.4 ±4.9	51.8 ±6.0	51.6 ±2.5	51.2 ±2.5	52.7 ±5.9	51.4 ±5.2	50.5 ±4.0	47.1 ±4.6	46.4 ±3.6	46.8 ±2.0	44.1 ±3.7	37.5 ±2.6
			51.4 ± 3.9				49.7 ± 5.7				44.0 ± 4.62			
pHa	7.330 ±0.83	7.261 ±0.83	7.328 ±0.067	7.336 ±0.059	7.326 ±0.070	7.328 ±0.060	4.304 ±0.047	7.318 ±0.062	7.350 ±0.065	7.346 ±0.033	7.371 ±0.054	7.384 ±0.058	7.408 ±0.078	7.486 ±0.127
			7.329 ± 0.059				7.330 ± 0.053				7.410 ± 0.085			
$P\bar{v}O_2$ torr	45.6 ±10.2	49 ±9.8	50.2 ±8.4	50.3 ±7.5	47.6 ±5.9	52.5 ±8.5	52.7 ±8.8	54.5 ±7.7	51.5 ±7.8	55.4 ±12	47.6 ±8.0	44.9 ±8.4	49.2 ±9.7	48.2 ±10.9
			50.1 ± 7.24				54.0 ± 8.7				47.5 ± 8.7			
$P\bar{v}CO_2$ torr	46.6 ±4.68	49.2 ±5.02	49.2 ±5.72	49.3 ±3.52	48.4 ±1.81	46.9 ±3.09	46.9 ±7.66	47.3 ±7.07	46.5 ±7.64	44.8 ±4.54	45 ±1.41	43.6 ±5.59	39.4 ±3.50	39.1 ±4.85
			48.45 ± 3.6				47.05 ± 6.56				41.9 ± 4.57			
pHv	7.296 ±0.89	7.27 ±0.092	7.346 ±0.073	7.358 ±0.066	7.364 ±0.085	7.338 ±0.063	7.318 ±0.046	7.325 ±0.088	7.352 ±0.076	7.370 ±0.054	7.382 ±0.051	7.400 ±0.075	7.436 ±0.089	7.456 ±0.069
			7.351 ± 0.067				7.342 ± 0.064				7.418 ± 0.073			
△(a–v) O_2 ml %	2.446 ±1.25	2.12 ±0.59	1.87 ±0.24	2.29 ±0.28	2.14 ±0.94	2.18 ±0.41	1.32 ±0.72	1.61 ±0.81	1.78 ±0.73	1.76 ±0.30	2.17 ±0.77	2.58 ±0.83	2.47 ±0.73	2.43 ±0.91
			2.14 ± 0.559				1.67 ± 0.61				2.34 ± .077			

Anesth Analg 57:470-477, 1978

TABLE 3

Peak Pressure, Total Static Compliance, Functional Residual Capacity, and Venous Admixture at Different Respiratory Rates and Tidal Volumes

(Mean Values ± 1 SD)

	Control	Apnea	TV-3				TV-10				TV-15			
RR breaths · min^{-1}	16	0	0.66	1	2	4	0.66	1	2	4	0.66	1	2	4
Peak pressure (cm H_2O)	15.5 ±4.7		8.3 ±1.5	8.65 ±3.1	9.3 ±2.4	9.2 ±2.2	22.9 ±2.6	23.9 ±0.9	27.0 ±3.8	25.1 ±3.7	33.6 ±3.1	31.4 ±3.7	36.6 ±3.4	28.9 ±3.4
			8.68 ± 2.22				24.7 ± 3.13				31.3 ± 3.6			
Total static compliance (ml · cm H_2O^{-1})	10.8 ±2.62	8.8 ±2.10	7.9 ±4.0	8.6 ±3.3	6.4 ±3.6	7.6 ±4.1	9.7 ±2.6	10.0 ±1.4	10.0 ±2.8	10.7 ±2.9	11.6 ±4.9	12.6 ±4.3	12.3 ±4.6	13.0 ±4.4
			7.61 ± 3.56				10.16 ± 2.20				12.34 ± 4.16			
FRC (ml kg^{-1} BTPS)	32.7 ±8.9	25.6 ±6.1	20.3 ±3.3	22.2 ±7.3	20.9 ±1.88	20.7 ±1.06	26.4 ±2.6	27.4 ±2.2	27.1 ±3.4	25.7 ±2.2	31.1 ±5.3	31.6 ±5.2	32.9 ±6.9	32.7 ±6.4
			20.8 ± 3.63				26.67 ± 2.52				32.03 ± 5.25			
$\dot{Q}_{VA}/\dot{Q}_T$	0.268 ±0.18	0.30 ±0.17	0.37 ±0.11	0.34 ±0.07	0.38 ±0.12	0.36 ±0.11	0.22 ±0.20	0.21 ±0.09	0.21 ±0.11	0.19 ±0.11	0.24 ±0.11	0.21 ±0.14	0.11 ±0.11	0.14 ±0.11
			0.357 ± 0.10				0.22 ± 0.11				0.16 ± 0.11			

ing all CO_2 produced), it becomes possible to maintain prolonged apnea. We have shown this during our control studies, as well as in our earlier study,[17] where apnea was maintained for 24 hours with normal blood gases and full recovery.

We found a consistent respiratory effect for CO_2 removal through the natural lungs only at TV-15 ventilation, which increased with the respiratory rate.

While the $Paco_2$ was steady during the LFPPV-ECCO$_2$R, our results showed a great variability of PAo_2 among the study periods. It has been established that during normal breathing with room air, the composition of alveolar gas becomes mainly a function of alveolar ventilation. During apnea, the gas composition in the natural lungs was totally controlled by the CDML; we previously showed that this control is through P_{N_2} in the CDML (ie, the P_{N_2} in the CDML is equal to the P_{AN_2} and PA_{N_2}).[17] TV-3 ventilation appears to be mainly a "dead-space" ventilation; in 3 out of 5 sheep the expired P_{CO_2} was zero. The relatively high PAo_2 found at TV-3 (mean, 280 torr) reflects nitrogen washout by the excess O_2 entering the trachea through the Teflon catheter, with only dead-space ventilation.

However, during the TV-10 and TV-15 ventilation, the lower PAo_2 is due to the supply of some nitrogen when ventilating with room air.

We would like to point out the paradoxical finding of higher P_{CO_2} and lower pH in arterial blood compared to pulmonary arterial blood. This is due to the acidification of blood by oxygenation of hemoglobin. The CO_2 content of the pulmonary arterial blood virtually equals the arterial CO_2 content, since little or no CO_2 is removed by the natural lungs. At constant total CO_2 in the blood, lowering pH by hemoglobin oxygenation results in raising P_{CO_2}.

While low-frequency positive pressure breathing alone has little or no respiratory meaning, the mechanical inflation of the lungs has great effect on the lung volumes and compliances. This effect is not related to the frequency, but to tidal volume (fig 3). During apnea FRC fell to about 80% of control values, and during the subsequent TV-3 ventilation it was approximately 60% of control. With TV-10 and TV-15 ventilation, at all RR, lung volume and compliance returned to control values.

The mechanism responsible for the change in FRC, ie, alveolar collapse, is not clear. The effects of anesthesia and paralysis on FRC[18] and on diaphragmatic mechanics[19] have been well documented in man. Preliminary studies in our laboratory immediately after anesthesia and paralysis followed by apneic oxygenation in a plethysmograph showed a sudden small change in FRC, followed by a steady continuous decrease with time. A fall in FRC did not occur with LFPPV-ECCO$_2$R at TV-10 and TV-15. Intermittent sighing during IPPB in man also is known to prevent a decrease in FRC.[20] A rise in FRC resulted in a decrease in venous admixture, but no linear relationship could be demonstrated.

We have not explored the long-term effects of LFPPV-ECCO$_2$R. However, preliminary experiments of LFPPV-ECCO$_2$R for 24 hours confirm our present results.

The main function of mechanical inflation of the lungs in this study was to maintain lung volumes rather than to provide for CO_2 and O_2 exchange; this was successful in TV-10 and TV-15 ventilation, but not successful at TV-3 ventilation. The RR of 1 breath every 90 seconds was the lowest setting of the ventilator; however, it might be possible to lower the RR to once every 2 or 5 minutes and still maintain the basal FRC. This is suggested from our earlier studies when the FRC returned to normal after 5 minutes of manual ventilation following 24 hours of apnea.[17] These findings could become useful in the understanding and management of patients on MV.

As described here, LFPPV-ECCO$_2$R was used for controlled ventilation in paralyzed animals. No doubt the CDML can also be used in conjunction with IMV to permit low-frequency positive pressure ventilation in spontaneously breathing patients, including those in whom IMV at a low frequency may be desirable but not now possible because of inability of spontaneous respiration to adequately remove CO_2.

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PULMONARY FUNCTION AFTER TRANSFUSION

Ventilatory volumes, blood gases, and other aspects of pulmonary function were measured before and after intraoperative transfusion in 16 patients who had undergone operation under general anesthesia. One group of 8 patients was transfused with an average of 1275 ml of stored blood passed through a standard nylon-mesh filter (SF group). Another group of 8 patients was transfused with an average of 1375 ml of stored blood passed through a dacron-wool filter (DWF group).

Since respiration was depressed slightly by preanesthetic sedation, a lowered expired minute ventilation (V_E) and tidal volume (V_T) and elevated $Paco_2$ and respiratory dead-space ratio (V_D/V_T) were observed in both the SF and DWF groups before anesthesia and transfusion. After recovery from anesthesia, V_D/V_T remained high and $Feco_2$ decreased in the SF group. In contrast, V_D/V_T decreased almost to normal and $Feco_2$ remained normal in the DWF group. Physiological shunt (Qs/Qt) tended to decrease after anesthesia and transfusion in both groups. The ventilation-perfusion ratio increased markedly for the SF group after transfusion. The data suggest that pulmonary microembolism occurs after transfusion of stored blood with a standard nylon-mesh filter. *(Takaori M, Nakajo N, Ishii T: Changes of pulmonary function following transfusion of stored blood. Transfusion 17:615-620, 1977)*

Effects of pH on Protein Binding of Lidocaine

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Protein binding of lidocaine (2.5, 5, 10, and 20 μg/ml) in fresh plasma was studied from pH 5.6 to pH 9.8. Percent binding of lidocaine was inversely related to hydrogen-ion and lidocaine concentrations.

Key Words — PROTEIN, binding. ACID-BASE EQUILIBRIUM, pH. ANESTHETICS, local, lidocaine.

LOCAL anesthetics exist in plasma in several forms: ionized, unionized, free, and bound. Plasma and tissue binding is extensive and constitutes the major pool or reservoir of local anesthetics in the body. Toxicity of local anesthetics, however, is related to the concentration of the free drug only.[1] Factors which affect binding (plasma or tissue) should also affect toxicity because of resultant changes in the free form of local anesthetics.[2-5] Englesson et al,[3] using 6 local anesthetics, demonstrated that an increase in CNS toxicity occurred with respiratory acidosis. Since toxicity is related to free drug concentration, these studies suggest a pH dependence of free drug concentration. The present study was undertaken to quantitate the magnitude of change in the bound-free equilibrium that occurs with changes in pH and to determine if the CNS toxicity changes previously reported correlate with the pH-induced changes in the binding of local anesthetic.

METHOD

Fresh plasma was separated from heparinized blood drawn from the authors on the morning of each study. The donors had clinically normal protein concentrations and electrophoretic patterns, and there was no variation in binding between donors for comparable samples. Crystalline lidocaine hydrochloride was added to the plasma samples to produce lidocaine concentrations of 2.5 to 20 μg/ml. Ultrafiltration[6,7] of each 10-ml aliquot of plasma was carried out using an Amincon Model 12 stirred cell with a PM 10 ultrafiltration membrane. This membrane passes compounds with a molecular weight of less than 10,000 and thus does not pass protein-bound drugs. Plasma pH was adjusted either by using fixed CO_2/nitrogen mixtures to produce pH 7.0 or 7.6 or by adding microlitre volumes of sodium hydroxide or hydrochloric acid to plasma samples. The cells were pressurized to 50 psi with the nitrogen-CO_2 mixture in the case of the former and with nitrogen in the latter case. pH in the cell was measured before and after filtration. Lidocaine concentration was determined by gas chromatography[8] in the original plasma and in the first 3 aliquots of 0.5 ml by duplicate determinations. All ultrafiltrates were protein-free by the Ames protein dipstick (negative with protein concentrations of less than 10 mg/dl). All studies were done at 21 C.

In order to determine whether binding affinity or the number of binding sites was primarily affected by pH change, the data were further evaluated using a Scatchard plot (fig 1), as described by Rosenthal.[7]

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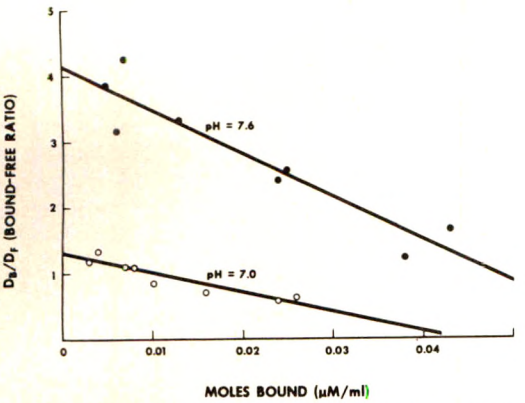


FIG 1. Bound/unbound ratio of data from table 1 plotted against moles bound at pH 7.0 and pH 7.6. The slopes of these lines indicate binding affinity, and the Y-intercept gives the relative number of binding sites.

With this technic, the ratios of the molar concentrations of bound to unbound drug are plotted against the molar concentrations of bound drug.* The slope of the resulting line is the affinity constant (k), and the Y-intercept indicates the relative number of binding sites. Since the nature of local anesthetic binding in human plasma is not known, the term np is used to indicate the relative number of binding sites.

RESULTS

The binding of lidocaine determined at pH 7.6 and 7.0 is listed in table 1. As pH decreases, binding also decreases. A pH change from 7.6 to 7.0, for example, changes lidocaine binding from 70% to 50% bound at 5 μg/ml plasma concentration. The Scatchard plot (fig 1) of these data suggests that as pH decreases from 7.6 to 7.0 there is a marked decrease in the affinity of lidocaine binding (k) and a moderate decrease in the number of lidocaine binding sites (np).

The plasma binding of lidocaine over a wide pH range was found (table 2) to follow a sigmoid curve (fig 2) which shifts slightly with changes in lidocaine concentration. Lower values for binding are associated with higher drug concentrations and higher hydrogen-ion concentrations. Maximum binding changes take place over the physiologic pH range.

TABLE 1
Lidocaine Concentrations (μg/ml) at pH 7.0 and 7.6

pH 7.0			pH 7.6		
Original plasma concentration	Protein-free filtrate concentration	Bound (%)	Original plasma concentration	Protein-free filtrate concentration	Bound (%)
19.03	7.38	38.8	19.72	12.38	62.8
17.93	8.25	46.0	19.39	11.46	59.1
10.72	4.59	42.8	9.71	6.92	71.3
6.20	2.96	47.8	9.68	7.17	74.1
4.45	2.46	55.4	4.94	3.36	68.0
3.76	2.16	57.5	4.78	3.65	76.4
2.07	1.30	62.8	2.33	1.95	83.6
1.61	0.91	56.8	2.34	1.80	77.0
			2.03	1.52	75.0
			1.60	1.31	82.0
$k = 29.8$ $np = 0.044$ correlation coefficient (r value) = 0.931			$k = 65.6$ $np = 0.063$ correlation coefficient (r value) = 0.935		

DISCUSSION

Most drugs are bound to some extent to plasma proteins, usually to albumin; however, some drugs (lidocaine) are bound to globulin. The nature of this binding is such that it is readily reversible and serves as a reservoir for the drug in the body. Although the binding occurs at charged sites on the protein molecule, the number of binding sites and the affinity of each is influenced by many factors. The percentage of a given drug bound to protein depends on the concentration of that drug, the concentration of the protein, the number of binding sites on the protein, and the affinity constant for the binding relationship. Other factors, such as temperature and pH, can also affect binding and/or the number of binding sites. In addition, the bound drug reservoir includes not only plasma protein and tissue bound drug, but also that bound to other substances (such as red cells or lipoproteins), as well as that which is physically dissolved in lipids.[7] However, regardless of the nature of the binding process, bound drug constitutes a major pool in the body for most local anesthetics.[9] A small

*Assuming $P + D \rightleftarrows PD$

then $k = \frac{[PD]}{[P]\ [D]} = \frac{D_b}{(np - D_b)\ D_f}$

and $\frac{D_b}{D_f} = npk - D_b k$

where P = protein, D = drug, D_b = molar concentration of bound drug, D_f = molar concentration of unbound (free) drug, n = number of binding sites/molecule of protein, p = molar concentration of protein, k = affinity constant

TABLE 2
Plasma Binding from pH 5.6 to 9.8* for Lidocaine Concentrations of 5, 10 and 20 μg/ml

5.0 μg/ml lidocaine		10.0 μg/ml lidocaine		20 μg/ml lidocaine	
pH	Bound (%)	pH	Bound (%)	pH	Bound (%)
9.60	76.8	9.80	75.7	9.40	71.8
9.30	80.1	9.00	72.2	9.21	71.4
8.76	72.7	8.50	67.4	8.62	70.8
8.45	72.8	8.21	68.3	8.40	64.7
7.68	65.9	8.00	64.8	7.70	53.8
7.60	59.4	7.60	55.0	7.60	41.2
7.60	52.9	7.60	54.5	7.60	53.8
7.42	46.1	7.22	43.1	7.56	47.6
7.40	51.2	7.00	27.5	7.50	43.6
7.10	47.0	7.00	24.6	7.41	45.4
7.00	34.7	6.70	27.0	7.31	36.0
7.00	34.8	6.00	22.8	7.18	40.29
6.50	27.8	5.61	21.8	7.00	30.15
6.00	31.3	5.58	17.6	7.00	23.01
5.60	17.3			6.40	23.3
5.20	17.6				

*pH was varied by addition of microlitre volumes of NaOH orHCl to 10-ml plasma samples.

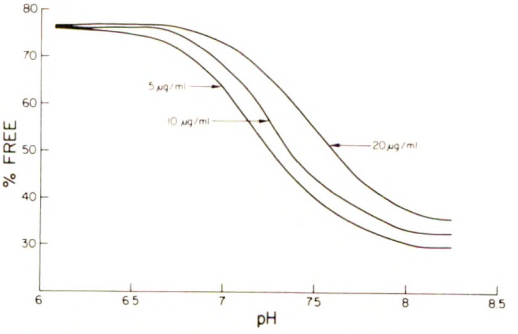


FIG 2. Percentage of free (unbound) lidocaine plotted against pH. Curves are drawn from data in table 2. As hydrogen-ion and/or lidocaine concentrations increase, binding decreases.

shift in the percentage of drug bound (plasma and tissues) will produce a relatively large increase in the amount of free drug available. Other drugs can compete with local anesthetics for plasma binding sites;[10] however, the importance of this displacement has been questioned.[11]

The results of this study show that pH does affect protein binding of lidocaine as measured in plasma. Furthermore, the physiologic pH range is normally at the point where small changes in pH would produce the largest changes in binding. Decreases in pH such as that produced by respiratory acidosis would result in an increase in the free drug available in plasma;[12] and, assuming plasma and tissue binding are similar, an increase in free drug at the active site. Such changes are consistent with the increase in CNS toxicity from CO_2 accumulation, although other pH-induced changes may also contribute.

The decreased binding with acidosis observed in this study and the associated large increase in the ionized form of free drug with acidosis support the hypothesis that the intracellular ionized form of lidocaine is the toxic form in the central nervous system as well as the active form in the peripheral nervous system.

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The Hepatoprotective Effect of Oxygen During Halothane Anesthesia

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The effects of halothane anesthesia on liver function, as reflected by postanesthetic changes in serum glutamic pyruvic transaminase (SGPT) levels, were evaluated in 2 groups of 40 patients. All patients had 2 halothane anesthetics. In 1 group, both anesthetics were administered at 1 atmosphere pressure with 30% O_2 in the inspired air. In the 2nd group, both anesthetics were administered at 2 to 3 atmospheres (absolute) of pressure with 97 to 98% O_2 in the inspired air. While the SGPT levels remained within the normal range in all cases, there was a significant rise in SGPT levels in patients undergoing surgery under 1 atmospheric pressure. Patients undergoing surgery at 2 to 3 atmospheres pressure (absolute) had SGPT levels which remained at low normal values. The difference in response of SGPT in the 2 groups was statistically significant. We conclude that increased O_2 tensions alter the normal response of SGPT to halothane anesthesia and that increased O_2 tensions appear to protect the liver from possible adverse responses to halothane or its metabolites.

Key Words—ANESTHETICS, volatile, halothane. LIVER, function. OXYGEN, hyperbaric. HYPERBARIA, oxygen.

ALL reported cases of hepatic failure suspected of being due to halothane have occurred following anesthesia at normal atmospheric pressures. We have not seen a case of halothane hepatitis following halothane-O_2 anesthesia under hyperbaric conditions of 2 or 3 atmospheres (absolute). Widger et al[1] have suggested that hypoxia might alter halothane metabolism with release of inorganic fluoride and other unidentified metabolites. It is possible that these unidentified products could be the cause of halothane hepatitis, and that adequate oxygenation could inhibit this pathway.

During the last 4 years, we followed 2 groups of patients, each of which was exposed to halothane on 2 occasions within a period of 2 weeks, under conditions of differing inspired O_2 tension. Our aim was to compare the incidence of hepatic dysfunction which might occur in these 2 groups of patients.

METHODS

The patients were assigned to 2 groups, each containing 40 patients, according to the O_2 tension maintained during anesthesia. Patients in both groups underwent halothane anesthesia on 2 occasions. Persons suffering from chronic cardiac failure or those who had a prior history of liver dis-

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ease were excluded from the study. With few exceptions, the body weight of both groups of patients was above average. Complete liver function studies were performed both prior to and after surgery. We elected to evaluate liver dysfunction by measuring serum glutamic pyruvic transaminase (SGPT) levels, pre- and postoperatively. SGPT estimation was chosen as a sensitive index of postoperative hepatic dysfunction.[2] None of the operations was performed on the upper abdomen.

Group A consisted of 40 neurosurgical patients (age range 30 to 60 years) who were anesthetized under normal atmospheric conditions, O_2 concentrations in the inspired air being maintained at 30%. Eight patients (20%) were hypertensive; 10 (25%) had diabetes mellitus. Their diseases were controlled at the time of the study. The 1st surgical procedure consisted of a diagnostic angiogram lasting an average of 2 hours. The 2nd procedure, which followed within 2 weeks, was a craniotomy lasting 6 to 8 hours.

Group B patients (age range 35 to 80 years) included 24 patients (60%) with hypertension and 20 (50%) with diabetes. Four patients (10%) had both diabetes and hypertension. In this group of patients, both primary and secondary surgery was vascular (femoral popliteal or aortobifemoral bypass procedures followed by amputation, sympathectomy, or carotid endarterectomy). These procedures varied from 1 to 4 hours in duration.

Premedication in all patients consisted of morphine sulfate (10 mg) and secobarbital (100 mg) or diazepam (10 mg) with atropine sulfate 0.3 to 0.4 mg by IM injection, 1 hour prior to surgery.

Group A Patients — Anesthesia was induced with sodium thiopental 200 to 300 mg IV, followed by succinylcholine chloride 80 to 100 mg IV for endotracheal intubation. Maintenance of anesthesia was with halothane 1% to 3% in N_2O (4 l/min) and O_2 (2 l/min). Relaxation was provided by pancuronium bromide (average dose 12 mg) or d-tubocurarine (average dose 66 mg). Patients were artificially ventilated with a tidal volume of 10 ml/kg. Pao_2 in this group averaged 110 mm Hg and $Paco_2$ 32 mm Hg. Anesthesia for the second surgery was the same as for the first.

Group B Patients — Anesthesia was induced with sodium thiopental 200 to 300 mg IV or diazepam 10 mg IV, followed by succinylcholine chloride 80 to 100 mg IV for endotracheal intubation. Maintenance of anesthesia was with 1% to 3% halothane in O_2 (8 l/min). Relaxation was provided by pancuronium bromide (average dose 8 mg). Respirations were controlled, with tidal volumes of 8 ml/kg. The patients in this group were operated upon at 2 to 3 atmospheres pressure (absolute). At 3 atmospheres pressure, Pao_2 averaged 1800 mm Hg and peripheral venous Po_2 was approximately 600 mm Hg. The same anesthetic management was used for the 2nd surgical procedure.

SGPT levels in all patients in the study were obtained from their charts. These were ordered routinely by the surgical staff 1 day preoperatively and 5 to 7 days postoperatively. This was repeated for the 2nd surgical procedure (ie, 1 day before the 2nd procedure and on the 5th to 7th day postoperatively). SGPT was measured as part of a 12-channel autoanalyzer technic (normal values 6 to 53 $m\mu$/ml).

RESULTS

Clinical manifestations of hepatocytotoxicity following halothane anesthesia were not observed in either group of patients. SGPT levels did not exceed normal values at any time in either group. However, a distinct pattern in SGPT values was noted after both primary and secondary exposure to halothane under normal atmospheric and hyperbaric conditions.

The changes in SGPT levels for each individual in the study following the 1st operation are shown in fig 1 and following the 2nd operation in fig 2. The figures suggest that changes in SGPT levels are a function of the original preoperative levels. Thus, before differences due to the use of halothane can be judged for significance, the figures must be adjusted for differences in initial SGPT levels in the 2 groups. Using the analysis of covariance, the change in SGPT level was shown to be 0.66 $m\mu$/ml per unit increase in preoperative SGPT levels. This slope was the same for both normobaric and hyperbaric groups. It was statistically significant, $t = 9.15$ ($p<0.01$).

Comparisons of changes in SGPT under normobaric and hyperbaric conditions are shown in tables 1, 2, and 3. Patients under normal atmospheric conditions had an average increase in SGPT of +9.38 $m\mu$/ml following the 1st operation, while those under

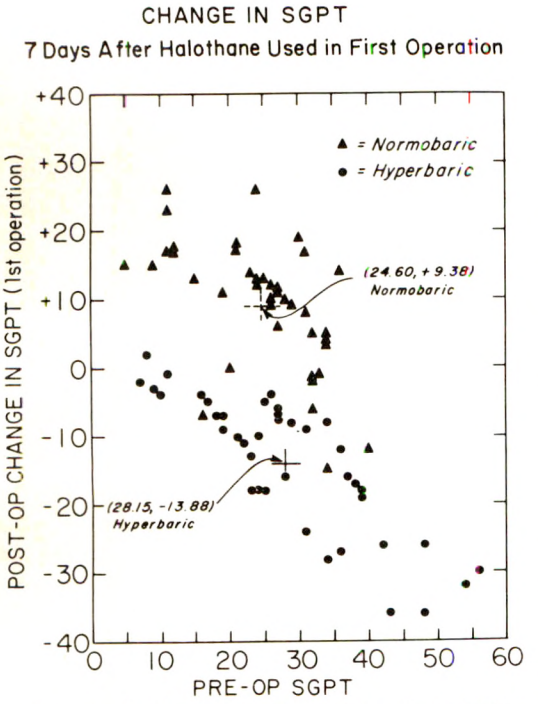


FIG 1. Scatter plot of postoperative SGPT changes versus preoperative SGPT values for the 1st operation in normobaric and hyperbaric patients

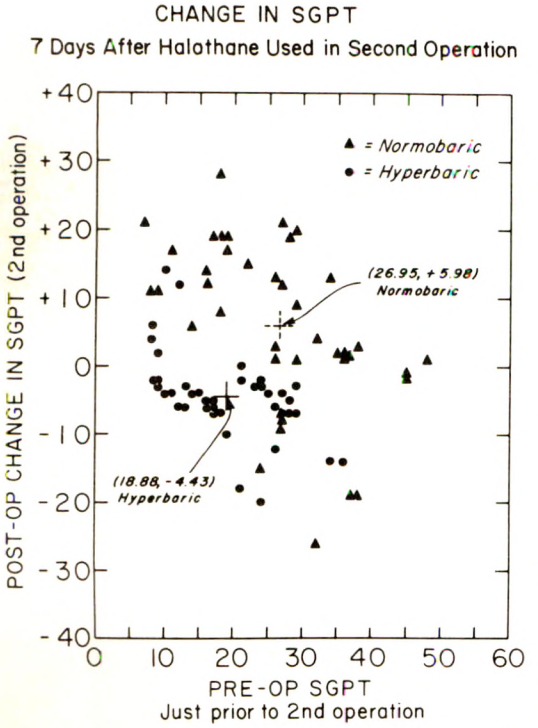


FIG 2. Scatter plot of postoperative SGPT changes versus preoperative SGPT values for the 2nd operation in normobaric and hyperbaric patients

TABLE 1
Changes in SGPT: First Operation

Groups	Preoperative	Postoperative
Normobaric	$\bar{y}$ = 24.60	$\bar{\Delta}$ = +9.38
(n = 40)	s = 8.66	s = 9.48
Hyperbaric	$\bar{y}$ = 28.15	$\bar{\Delta}$ = −13.88
(n = 40)	s = 12.37	s = 10.11

Δ = Postoperative SGPT — preoperative SGPT

The mean ($\bar{y}$) and standard deviation (s) of preoperative values for SGPT and the change in SGPT values postoperatively expressed as the mean ($\bar{\Delta}$) following the 1st operation in normobaric and hyperbaric patients

TABLE 2
Values for SGPT Prior to First and Second Operations (Mean ± SD)

Groups	Before 1st operation	Before 2nd operation
Normobaric	$\bar{y}$ = 24.60	$\bar{y}$ = 26.95
(n = 40)	s = 8.66	s = 9.76
Hyperbaric	$\bar{y}$ = 28.15	$\bar{y}$ = 18.88
(n = 40)	s = 12.37	s = 7.76

Abbreviations as in Table 1

TABLE 3
Changes in SGPT: Second Operation

Groups	Preoperative	Postoperative
Normobaric	$\bar{y}$ = 26.95	$\bar{\Delta}$ = +5.98
(n = 40)	s = 9.76	s = 12.39
Hyperbaric	$\bar{y}$ = 18.88	$\bar{\Delta}$ = −4.43
(n = 40)	s = 7.76	s = 6.46

Abbreviations as in Table 1

hyperbaric conditions showed a decrease of −13.88 mμ/ml (table 1). This difference of 23.26 mμ/ml (after adjusting for the small difference in preoperative SGPT in the 2 groups) was statistically significant, t = 13.50 ($p<0.001$).

Table 2 shows that the mean SGPT level of hyperbaric patients decreased in the week between the 2 operations, while that of the normobaric patients returned to the SGPT levels which existed prior to the 1st operation. The preoperative SGPT levels in the hyperbaric patients prior to the 2nd operation were significantly less than the preoperative SGPT levels in the same patients prior to the 1st operation, t = −4.02 ($p<0.01$). The other 3 SGPT preoperative

values in table 2 are not significantly different. This same result can be seen in comparing fig 1 with fig 2; the dispersion of the normobaric patients relative to the preoperative levels is the same in both figures. However, the hyperbaric patients' preoperative values shown in fig 2 are crowded together at a lower level (average = 18.88) than they are in fig 1 (average = 28.15).

Table 3 shows that even with a lower preoperative SGPT level at the time of the 2nd operation, hyperbaric patients showed a further significant drop in the SGPT level when compared with the SGPT level in normobaric patients (ie, hyperbaric $\bar{\Delta} = -4.43$ compared to normobaric $\bar{\Delta} = +5.98$). This was statistically significant, $t = 4.71$ ($p<0.001$).

DISCUSSION

This study compared possible liver dysfunction, expressed by SGPT levels, in 2 groups of patients who were twice exposed to halothane under conditions of differing O_2 tensions. In patients given halothane anesthesia at 1 atmosphere, SGPT values changed significantly while remaining within normal limits, after both 1st and 2nd exposures to halothane. In patients anesthetized under hyperbaric conditions, SGPT levels remained unchanged or at a lower level after both 1st and 2nd exposures.

Liver damage which occurs following anesthesia may be related to diminished blood flow through the liver, resulting in a decreased O_2 supply. An increased arterial CO_2 tension or a decreased O_2 tension has also been shown to produce a catecholamine response with subsequent vasoconstriction and a decrease in liver blood flow.[3] Splanchnic blood flow and cardiac output measured in dogs during halothane anesthesia with controlled ventilation showed marked reduction in splanchnic blood flow due mainly to a reduction in cardiac output.[4] Hepatic blood flow is known to be significantly decreased during clinical anesthesia,[5] halothane producing a greater decrease than diethyl ether; but the type of surgery is also of importance, major surgery being associated with significantly greater decrease in hepatic blood flow than is minor surgery. Price et al,[6] by measuring hepatic venous O_2 and the production of lactate by the liver, found, however, no evidence of hepatic hypoxia in healthy anesthetized individuals. On the other hand, venous Po_2 may not be an accurate index of tissue Po_2, usually being above the Po_2 levels which actually exist in tissues.[7]

Van Dyke and Wood[8] found that radioactivity from ^{14}C-labeled halothane became bound to cellular phospholipid and proteins in isolated perfused rat livers when ^{14}C halothane was present in the perfusate. This binding was proportional to the metabolism of halothane. Binding was also inversely proportional to the rate of perfusion, and was covalent or irreversible. The authors concluded this binding was the result of the production of an intermediate metabolite. Van Dyke and Gandolphi[9] have also shown that reduction of inspired O_2 during halothane anesthesia in the rat is associated with increased levels both of fluorides in the blood and reductive metabolites in the urine, with an increased incidence of liver damage. The possibility that increased levels of reductive products of halothane metabolism observed during hypoxia may be associated with hepatotoxicity stands in contrast to the failure of previous studies using oxidative products alone or in combination with human specific protein or human serum albumin to prove the existence of a cell-mediated immunologic response in humans with unexplained hepatitis following halothane.[10]

The elevation (though still within normal limits) of SGPT in patients anesthetized at 1 atmosphere could be indicative of low liver blood flow and low hepatic tissue O_2 tensions which, although normally innocuous to the hepatocyte, could lead to the accumulation of reductive halothane products which might adversely affect the liver. The effect of O_2 is observed in patients anesthetized under hyperbaric conditions in whom SGPT levels were maintained at lower normal limits, even lower than preoperative values. Our clinical observation suggests that during normal atmospheric conditions minor changes in liver function occurred which were manifested by changes in SGPT levels. Under hyperbaric conditions, on the other hand, there was abundant O_2, balancing possible low or nonuniform regional microflow and low tissue-O_2 concentration, as may occur in the corner located between 2 capillaries at the venous end of the hepatic lobule. This was manifest by lack of SGPT elevation.

We conclude from these studies that O_2 at increased tensions of 2 to 3 atmospheres has a protective effect on the liver during exposure to halothane, possibly by inhibiting the formation of the reductive products of halothane.

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PROPRANOLOL REBOUND

To assess the effects of sudden withdrawal of propranolol on inpatients with coronary artery disease, 102 patients admitted for cardiac catheterization were evaluated. Criteria for inclusion in the study were angiographically documented coronary artery disease, propranolol therapy at a mean daily dose of at least 80 mg, and abrupt discontinuation of propranolol therapy before catheterization. There were 55 patients (mean age 52.5) who discontinued propranolol therapy (mean daily dose 127 mg), and a control group of 47 patients (mean age 53) who continued to receive propranolol (mean daily dose 143 mg). The criteria for morbidity were death, myocardial infarction, or change in pain pattern. In the withdrawal group there were no deaths, 1 myocardial infarction judged to be related to catheterization, and only 1 instance of a change in pain pattern. Thus, propranolol rebound appears to occur infrequently among hospitalized patients with reduced activity. *(Shiroff RA, Mathis J, Zelis R, et al: Propranolol rebound: a retrospective study. Am J Cardiol 41:778-780, 1978)*

Lumbar Sympathetic Block with Bupivacaine: Analgesia for Labor

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Forty primigravidas were given a bilateral paravertebral lumbar sympathetic block during stage I of labor using 10 cc of 0.5% bupivacaine and 1:200,000 epinephrine on each side. Good analgesia was obtained in 38 patients with maximal effect 7.5 ± 3 minutes after blockade. Maternal mean blood pressure and pulse were unchanged, fetal well-being was not compromised, and labor progressed rapidly. Twenty-eight patients delivered prior to resolution of the block, while in the remaining 12 patients pain returned before delivery with analgesia having lasted 283 ± 103 minutes. In the former 28 patients, analgesia for expulsion was provided by pudendal, saddle block, or infiltration analgesia, whereas continuous lumbar epidural or caudal analgesia was utilized when remission preceded stage II. In comparison to continuous lumbar epidural analgesia, the procedure is technically more difficult, generally more painful, and requires a second anesthetic for delivery. It is concluded that bilateral paravertebral lumbar sympathetic block with bupivacaine provides reliable analgesia of long duration with a low incidence of undesirable side effects. However, its primary usefulness is in cases where continuous lumbar epidural analgesia is refused or contraindicated.

Key Words—ANESTHESIA, obstetric. ANESTHETIC TECHNICS, sympathetic block. SYMPATHETIC NERVOUS SYSTEM, paravertebral sympathetic block. ANESTHETICS, local, bupivacaine.

PARAVERTEBRAL lumbar sympathetic block was first described for use in obstetrics in 1927.[1] However, the mechanism of action was not greatly appreciated until 1933, when Cleland demonstrated that uterine and cervical visceral afferent sensory fibers join the sympathetic chain at L2-3.[2] Later authors reported the ease of administration of paravertebral sympathetic block, its reliability for producing analgesia during labor, and a low incidence of maternal side effects.[3-6] In addition, Hunter used tokodynamometry to demonstrate acceleration of the first stage of labor in 20 of 39 parturients given sympathetic blocks.[7] Significant detrimental fetal effects have not been reported.[6]

Although sympathetic-block analgesia is efficacious and relatively safe, its usefulness has been precluded by the short duration of action obtained with local anesthetic agents available in the past. We have re-examined the technic using the long-acting local anesthetic bupivacaine hydrochloride. Our results corroborate those cited before, except that in contradistinction to the earlier reports, the duration of analgesia with 0.5% bupivacaine was usually long enough. This report describes clinical features of this anesthetic technic in 40 parturients.

METHODS

Forty primigravidas with a mean age of 21.7 years and a mean gestation of 40 weeks received a bilateral paravertebral lumbar

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sympathetic block during the first stage of labor. They were all ASA I patients[8] and had unremarkable gestational histories except for a single patient at 28 weeks' gestation with premature rupture of membranes and early chorioamnionitis. Thirty-three patients were in the active phase of labor, as described by Friedman,[9] when cervical dilatation was 4 to 5 cm with uterine contractions occurring every 3 minutes and lasting more than 30 seconds. The remaining 7 patients were in the latent phase or had a dysfunctional labor pattern. All patients underwent continuous electronic monitoring of fetal heart rates and uterine contractions (Corometrics type III B) for at least 30 minutes before sympathetic block. Fetal heart rates were measured with scalp electrodes or external ultrasound transducers, and patients were excluded from the study if evidence of fetal distress existed. Baseline cervical dilatation, frequency of contractions, maternal blood pressure and pulse, skin temperature from the lower extremity, and fetal heart rates were recorded. An assessment of fetal heart rate baseline variability was made in those patients with direct scalp-electrode monitoring. Patients received an IV infusion of 500 ml of lactated Ringer's in 5% dextrose and H_2O prior to initiation of sympathetic blocks.

With patients in the sitting position, paravertebral sympathetic blocks were administered as described by Moore.[10] Following antiseptic preparation of the skin, an intradermal injection of 1% lidocaine was made bilaterally 4.5 cm lateral to the midpoint of the 2nd lumbar spinous process. A 10-cm, 22-gauge needle was introduced with a 20-degree cephalad direction to identify the second lumbar transverse process. The needle was then withdrawn to the skin and redirected beneath and 4.5 cm beyond the transverse process with a 10-degree mesiad angle. If the vertebral body was encountered, the needle was withdrawn and redirected laterally 5 to 10 degrees. Ten millilitres of 0.5% bupivacaine hydrochloride with 1:200,000 epinephrine were injected on each side.

Patients were then returned to the lateral position. The time from injection of the second side to maximum or complete uterine analgesia was noted. Frequency of contractions, maternal blood pressure and pulse, fetal heart rate, and skin temperature of the lower extremity were recorded every 5 minutes after blockade. Quality of maternal analgesia was ascertained by a scoring system from zero to 3, with zero representing no analgesia and 3 representing complete uterine analgesia. Scores of 2 or 3 were considered to represent satisfactory analgesia. The time from injection of the local anesthetic to complete cervical dilatation was noted, as was the time to recurrence of abdominal or back discomfort. Anesthesia for delivery was provided by pudendal, local-infiltration, or saddle-block analgesia. Continuous lumbar epidural or caudal blocks were administered when the sympathetic block remitted prior to the second stage of labor. Neonatal Apgar scores were assigned at 1 and 5 minutes. Data were analyzed with Student's t-test for paired samples. Significance was assumed when $p<0.05$.

RESULTS

Satisfactory analgesia was obtained in 38 patients: 31 had an analgesia score of 3. Onset of analgesia was rapid, with a mean time (± SD) to maximal analgesia of 7.5 ± 3 minutes. Twenty-eight patients delivered before analgesia wore off, and the duration of blockade in this group was not determined. In the remaining 12 patients (30%), the block wore off before delivery. The mean duration of uterine analgesia in this group was 283 ± 103 minutes, with a range of 180 to 450 minutes. Eight of these 12 patients were given continuous lumbar epidural analgesia; the remaining 4 received caudal anesthesia.

Following sympathetic blockade, significant changes in mean maternal blood pressure and pulse rate were not noted. However, significant (>20%) reduction in maternal blood pressure occurred in 2 patients, both of whom were in the supine position for vaginal examinations. The blood pressure returned to normal upon resumption of the lateral position. The mean increase in skin temperature of the lower extremity, 4.5 ± 1.8 C, was achieved within 25 minutes.

At the time of blockade, the mean cervical dilatation of the 33 patients in active labor was 4.8 ± 0.9 cm. There was no change in the frequency of contractions, and the mean time from block to complete cervical dilatation was 158 ± 92 minutes. In addition, mean fetal heart rates were not changed, and a significant alteration in the baseline variability of fetal heart rates was not seen in any patient. However, 1 patient required cesarean section for sustained fetal bradycardia occurring 150 minutes after the block. This event was believed by the at-

tending obstetrician to be secondary to umbilical-cord compression and unrelated to sympathetic block. This infant's Apgar scores were 8 and 9. Apgar scores for the entire group were 7.9 ± 1.3 and 9.0 ± 0.8 at 1 and 5 minutes, respectively.

DISCUSSION

Pain in the first stage of labor is largely due to distention of the cervix and lower uterine segment. The sensory fibers from the uterus and cervix travel with sympathetic nerves passing through the posterior cervical plexus (Frankenhauser's plexus) and the superior hypogastric plexus to enter the sympathetic chain at L2-3. They then ascend in the paravertebral sympathetic chain to enter the spinal cord via the white rami communicantes at the 11th and 12th thoracic levels.[2,11] Therefore, a conduction blockade of the sympathetic chain at the 2nd lumbar vertebra prevents transmission of afferent sensory impulses from the cervix and uterus and will provide analgesia during labor.[2-5]

The primary limitation to lumbar sympathetic block for labor has in the past been the short duration of analgesia. Shumacker et al obtained analgesia with 0.5% tetracaine, but the maximum duration was 4 hours.[3] Various concentrations of procaine and piperocaine yield an average duration of 90 minutes;[5] lidocaine produces analgesia for 90 to 180 minutes.[12] We utilized bupivacaine because of its long duration of action, its reliable sensory blockade, and its apparently low placental transfer.[13-17] Our results show that 0.5% bupivacaine with 1:200,000 epinephrine ensures a more acceptable duration of analgesia, for the mean analgesia time of 283 minutes far exceeds that of all previously studied agents. The effect of epinephrine on duration of sympathetic blockade with bupivacaine is questionable. In epidural blockade, epinephrine decreases the rate of maternal absorption of bupivacaine but does not prolong its effect.[18] We used epinephrine with the intention of lessening the absorption and placental transfer of bupivacaine, not to prolong its duration of action.

Notable features of bupivacaine sympathetic block were the rapid onset of action and high success rate of analgesia. Failure to obtain suitable analgesia in 2 of 40 patients compares favorably with a success rate of "over 90%," as noted by Bonica.[6] Since this technic produces no motor blockade, patients can move about freely and can "bear down" effectively in the second stage of labor. In addition, the progression of labor is rapid, as evidenced by the mean block to complete cervical dilatation time of 158 minutes seen in the 33 patients in active labor. This finding compares favorably with the duration of labor noted after continuous lumbar epidural analgesia with 0.5% bupivacaine.[19] Moreover, adverse effects of the technic on fetal heart rate were not observed. Thus, bupivacaine sympathetic block would apparently be more advantageous than paracervical block anesthesia, which has frequently been associated with fetal bradycardia.[20,21]

Bonica quotes a 15 to 20% incidence of "mild hypotension" after lumbar sympathetic blocks.[6] In our study, the 5% incidence of maternal hypotension, which responded rapidly to position change, is most acceptable. Our incidence of hypotension may be lower because patients were hydrated before blockade and because they were placed in the lateral position after blockade.

Although bilateral paravertebral sympathetic block can usually be completed within 10 minutes, it is generally more painful and technically more difficult than lumbar epidural analgesia. In addition, the use of sympathetic block for labor necessitates the administration of a second anesthetic for delivery. Continuous lumbar epidural analgesia not only provides good analgesia for vaginal delivery but also ensures successful anesthesia for cesarean section when necessary. Although the duration of analgesia with bupivacaine sympathetic block exceeds that observed after single-dose epidural blockade with bupivacaine,[19,22] the duration of analgesia was still insufficient in 30% of our patients. This finding substantiates our usual preference for continuous epidural anesthesia, especially for pitocin-induced labors, which have unpredictable durations.

As a result, our use of continuous lumbar epidural anesthesia and sympathetic blocks for labor has approximated a ratio of 10 to 1. We use sympathetic blockade primarily when epidural analgesia is contraindicated or refused. For example, one patient in this study underwent lumbar fusion 4 years prior to admission, making epidural blockade impossible. Two patients were nurses who refused spinal and epidural anesthesia but consented to sympathetic blockade. While

not allowing the flexibility of continuous lumbar epidural anesthesia, sympathetic block with 0.5% bupivacaine provides another mechanism to achieve analgesia for stage I of labor.

Perineal analgesia for stage II is usually provided after paravertebral sympathetic block with pudendal or saddle-block anesthesia. Pudendal blockade is preferred for spontaneous deliveries, whereas saddle block is utilized when forceps are indicated. We encourage our obstetricians to initiate pudendal anesthesia in the labor room when perineal discomfort becomes disconcerting.

It is noteworthy that total spinal anesthesia has been reported in 2 patients receiving lumbar sympathetic blockade.[23] Meticulous attention to detail should prevent this complication. Inadvertent penetration into the retroperitoneal space with subsequent hemorrhage has been reported in 3 patients who received a series of paravertebral blocks for treatment of peripheral vascular disease.[24] This complication was not mentioned in the literature we reviewed of lumbar sympathetic blocks for labor. Our incidence of intravascular needle placement is approximately 2%; hemorrhagic sequellae have not occurred. Furthermore, symptoms of maternal local anesthetic toxicity have not been encountered to date (in 325 cases). Due to possible increases in uterine contractility,[7] caution should be exercised regarding the use of this anesthetic technic in parturients with tetanic labor patterns or with evidence of uteroplacental insufficiency.

In conclusion, bilateral paravertebral lumbar sympathetic blockade with 0.5% bupivacaine and 1:200,000 epinephrine is an effective anesthetic technic for labor, yielding a high incidence of good uterine analgesia. The duration of sensory blockade with bupivacaine greatly exceeds the duration of blockade seen with other local anesthetic agents. In our study, uterine analgesia persisted throughout delivery in 70% of our primigravid patients. Labor progresses well, and the block is not commonly associated with maternal or fetal complications. However, hypotension can occur, and blood pressure must be monitored. Since continuous lumbar epidural analgesia is less painful, technically less difficult, and can be extended to provide analgesia for vaginal or abdominal delivery, bupivacaine sympathetic blockade is primarily utilized when continuous lumbar epidural analgesia is contraindicated.

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PREOPERATIVE ORAL ANTACID THERAPY

Presence of a gastric pH of less than 2.5 and a volume greater than 25 ml identifies patients "at risk" of developing perioperative acid-aspiration pneumonitis. Preoperative oral antacid therapy has been used effectively to reduce the number of emergency obstetric patients "at risk." Thirty-three nonobstetric adult patients requiring emergency surgery were selected to determine whether the protective effects of antacid therapy could also be derived in this group. Fourteen patients who received 30 ml of combined magnesium and aluminum hydroxide antacid had a gastric pH (mean ± SD) of 6.46 ± 0.5 and gastric volume of 21.5 ± 3.6 ml, with none "at risk," whereas 19 control patients had a mean pH of 3.71 ± 0.43 and gastric volume of 71.5 ± 16.5 ml with 42% "at risk." These data suggest that preoperative antacid therapy should reduce the incidence of acid aspiration and subsequent morbidity and mortality in patients requiring emergency surgery. *(White FA, Clark RB, Thompson DS: Preoperative oral antacid therapy for patients requiring emergency surgery. South Med J 71:177-179, 1978)*

Clinical Reports

Unsuspected Dilution of Anesthetic Gases Detected by an Oxygen Analyzer

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VENTILATORS are an important part of the equipment utilized by anesthesiologists in the operating room. Waterman et al[1] recently reported hyperventilation resulting from a tear in the bellows of an Ohio Fluidic Ventilator. We have encountered yet another problem from a tear in the bellows of this ventilator. We encountered higher than expected O_2 concentrations in anesthetic circuits secondary to perforations in the bellows.

Three times in the past 18 months, we have detected bellows perforations by unusually high O_2 concentrations observed using a Harris-Lake Sentry II Oxygen Analyzer placed in the inspiratory limb of the circle system. In each case there was a linear tear along an inner fold of the bellows. The first perforation measured 16 mm in length. In the second case there were two perforations, 2 and 4 mm in length, and in the third case there was a perforation 27 mm in length. In cases one and three the perforations were near the top of the bellows and were apparently spontaneous. In the second case the two small perforations were near the bottom of the bellows and were caused by abrasion from the bellows rubbing against the plastic pegs located in the bellows head assembly. In the first two of these cases the ventilator performed normally; however, in the case with the largest tear, it malfunctioned. In this latter case, with the ventilator set at a low inspiratory flow rate and the inspiratory pressure at its maximum, the bellows rose incompletely while the patient appeared to be well ventilated. In cases one and two, O_2 concentrations of 50 to 60% were measured in the breathing circuit when the gas machine was delivering N_2O 500 ml/min and O_2 300 ml/min. In case three, a reading of 70% O_2 concentration was observed with a delivery of N_2O 2 L/min and O_2 1 L/min. In each case the in-circuit O_2 concentration returned to the expected 30 to 35% after the ventilator was disconnected, and the patient was ventilated manually with the breathing bag. Correct calibration of the O_2 analyzer was confirmed in each case by exposure to room air and 100% O_2.

Ventilators of common usage in this country are of two types: those in which the bellows rises during exhalation, and those in which the bellows descends during exhalation. In a ventilator where the bellows rises during exhalation, a bellows perforation is easily detected. Here, the anesthetic gases leak *from* the breathing circuit and the bellows tends to collapse. However, in those ventilators with a bellows which descends during exhalation, a perforation may not be readily apparent, especially if the perforation is small. Here, the powering gas for the ventilator leaks *into* the breathing cir-

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cuit thereby diluting the anesthetic gases and augmenting the tidal volume.

There are three opportunities for detecting bellows perforations in the type of ventilator which we used. First, an unexpectedly high reading of the in-circuit O_2 analyzer may indicate a perforation. Second, a perforation can be detected by inspection during routine cleaning. Third, if the perforation is large enough, gross ventilatory dysfunction may occur.

Patient awareness during anesthesia is of concern to anesthesiologists. It is usually associated with the use of balanced anesthesia. With this technic it is important to maximize the benefits of N_2O by using high yet safe concentrations of N_2O, ie, 70%. If unrecognized dilution of the N_2O-O_2 mixtures occurs, the decrease in N_2O concentrations would result in less than expected levels of anesthesia and could contribute to awareness during anesthesia.

If a bellows perforation does occur, the use of an O_2 analyzer will not only help prevent inadequate oxygenation, but may also detect early perforations by indicating inadequate N_2O concentrations. This may prevent some instances of "awareness" during anesthesia.

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Hemodynamic Changes After Intercostal Nerve Block with Bupivacaine-Epinephrine Solution

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BUPIVACAINE is widely accepted as a safe, long-acting local anesthetic. Its use for intercostal blocks after surgical thoracotomies has been shown to decrease postoperative pain and improve pulmonary function.[1] Despite its relative safety and its reportedly minimal effect on the cardiovascular system, the following case reports illustrate that commercially prepared bupivacaine solutions containing 1:200,000 epinephrine, when used for intercostal blockade, may be associated with profound cardiovascular changes.

REPORTS OF TWO CASES

Patient 1—A 59-year-old man underwent multiple surgical procedures for repair of a hiatal hernia with reflux. The last procedure, a transthoracic fundoplication, was complicated postoperatively by a leaking esophagogastric junction. During the ensuing 10 weeks, the patient experienced mild respiratory distress and had roentgenographic evidence of mild congestive heart failure and extrapulmonic fluid. He was scheduled for re-exploration and repair of the leaking anastomosis. His past medical history was otherwise negative, and results from routine laboratory tests were within normal limits.

Operating room monitoring included ECG, esophageal temperature probe, esophageal

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stethoscope, a 20-gauge Longdwel* cannula inserted in the radial artery for measurement of arterial pressure, and a 5-Fr Swan-Ganz catheter inserted preoperatively into the pulmonary artery via the right internal jugular vein. Radial and pulmonary arterial blood pressures were monitored and recorded continuously. Pulmonary arterial wedge pressure readings were taken at least every hour.

Anesthesia was induced with 175 mg sodium thiopental and 120 mg succinylcholine chloride, IV, and the patient's trachea was intubated with a 7.0-mm soft cuff tube. Anesthesia was maintained with intermittent doses of fentanyl and pancuronium, IV, and 60% N_2O in O_2, by inhalation. Seven and one-half hours later, a serosal patch of the leak with drainage through a Roux-en-Y anastomosis was completed. Systemic arterial blood pressure had remained stable at approximately 125/80 torr, while pulmonary capillary wedge pressure varied between 13 and 17 torr. Just before closure of the chest, a total of 15 cc of 0.75% bupivacaine with 1:200,000 epinephrine was injected intercostally in 5 equally divided doses at multiple sites by the surgeon

Almost immediately a marked increase in intensity of heart sounds was noted through the esophageal stethoscope, and systolic radial artery blood pressure rose to over 200 torr (see figure). In less than 2 minutes the pressure fell rapidly, and within 8 minutes was approximately 50/30 torr. Arterial blood gas analysis at this time showed a pH of 7.32; Po_2 110 torr; and Pco_2 39 torr The calculated base deficit was 5 mEq/L. Systemic blood pressure failed to respond to IV administration of calcium chloride 1000 mg, ephedrine 25 mg, and sodium bicarbonate 44.6 mEq. A norepinephrine drip (4 mg in 500 cc of 5% dextrose in H_2O) was initiated to maintain normal pressure. Arterial blood pressure remained stable, but attempts to wean the patient from the vasopressor were unsuccessful after 30 minutes, despite adequate pulmonary capillary wedge pressures. The patient was transported to the surgical intensive care unit, where he required mechanical ventilatory support with low-rate intermittent mandatory ventilation (IMV) and low levels of positive end-expiratory pressure (PEEP). No evidence of myocardial infarction was found. He was weaned from the vasopressor 12 hours later and was extubated after 2 weeks of respiratory support.

Patient 2—A 43-year-old woman weighing 49 kg was scheduled to have a lobectomy to remove a coin lesion in the middle lobe of the right lung. Her past medical history was unremarkable except for a history of peptic ulcer disease and asymptomatic click murmur syndrome. She was given penicillin prophylactically against subacute bacterial endocarditis and was premedicated with morphine sulfate 6 mg, sodium pentobarbital 100 mg, and atropine 0.4 mg, IM. The patient was brought to the operating room, and after monitoring equipment was attached, anesthesia was induced with d-tubocurare 3 mg, sodium thiopental 250 mg, and succinylcholine chloride 120 mg, IV. Anesthesia was maintained with endotracheal 50 to 60% N_2O in O_2 and 0.6% halothane using a semiclosed circle absorption system.

The case proceeded uneventfully until the surgeon performed intercostal nerve blocks

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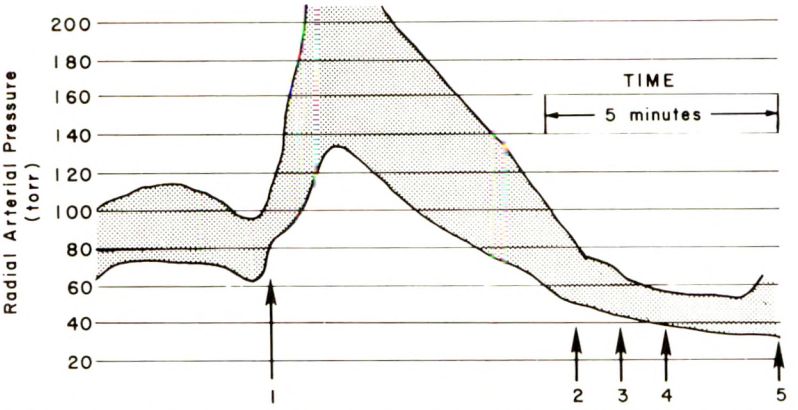


FIGURE. Plot of blood pressure recorded from the radial artery. (1) Bupivacaine 0.75% with 1:200,000 epinephrine (15 cc); (2) ephedrine sulfate 25 mg; (3) $CaCl_2$ 1000 mg; (4) $NaHCO_3$ 44.6 mEq; (5) norepinephrine drip 4 mg in 500 cc of 5% dextrose in H_2O.

at 5 levels, using a total of 15 cc of 0.5% bupivacaine with 1:200,000 epinephrine. When the needle was withdrawn from the last intercostal nerve blocked, a stream of arterial blood was noted to be coming from a previous injection site. The patient had frequent multifocal premature ventricular contractions, and her blood pressure rose from a relatively stable operative blood pressure of 100/60 torr to 170/120 torr. Halothane was discontinued and an IV bolus of 50 mg of lidocaine was administered. The premature ventricular contractions ceased, but over the next 20 minutes arterial blood pressure dropped progressively to 60/40 torr, although there had been no significant blood loss or ECG changes during this period. At this time estimated blood loss was less than 500 cc; fluid replacement had been 3000 cc of lactated Ringer's solution, one-third of which contained 5% dextrose. The patient's pressure remained low until she was transfused with a unit of whole blood, which increased her pressure to 95/60 torr. The postoperative hematocrit reading was 34 vol %, which was unchanged from the preoperative level; the postoperative 12-lead ECG also remained unchanged. The patient's postoperative course was uneventful.

DISCUSSION

Bupivacaine has been used for a wide variety of conduction anesthetics with apparent minimal effects on the cardiovascular system. Moore et al[2] reported only 15 systemic toxic reactions in a review of 11,080 bupivacaine anesthetics, and these were manifested by neurologic symptoms; no cardiovascular effects were reported. The cardiovascular effects described in our 2 case reports may have been the result of the epinephrine injected with the bupivacaine, causing acute hypertension followed by acute hypotension.[3] Failure of the blood pressure to return to normal after 30 minutes, however, suggests that bupivacaine may have played a cardiovascular-depressant role. Intercostal blocks differ substantially from other peripheral nerve blocks in producing higher blood levels of local anesthetic for a given dosage injected.[2,4,5] Moore et al[2] reported only 2 cases of systemic toxicity, both intercostal blocks, caused by peripheral absorption of bupivacaine in 11,080 nerve blocks of various types. An acute rise in bupivacaine level resulting from intravascular injection might increase the already high bupivacaine levels from absorption and might greatly increase the probability of obtaining toxic levels of bupivacaine.

Another unique feature of intercostal blocks is the possibility of an inadvertent spinal anesthetic caused by dissection of the local anesthetic along the intercostal nerve to the subarachnoid space. Such an occurrence would explain the hypotension which occurred in the present cases. Spinal anesthesia was unlikely in case 2, however; at the end of the operative procedure the patient was awake and able to move all extremities. Although patient 1 required prolonged respiratory support, he was never without spontaneous respiratory effort on IMV, which speaks against a total spinal anesthetic.

The possibility of bupivacaine toxicity from intercostal blocks may be increased by altered pharmacokinetics in individual patients. Those with heart failure have a higher incidence of lidocaine toxicity than those without because of a prolonged halflife of metabolism and distribution.[6,7] We feel that this mechanism may have led to elevated plasma bupivacaine levels in patient 1, who had both roentgenographic evidence and pulmonary artery wedge pressures compatible with the diagnosis of congestive heart failure. There was no evidence to suggest congestive heart failure in patient 2. Both patients, however, were under general anesthesia when the intercostal blocks were administered. Although we are not aware of a controlled study on the effects of general anesthesia on plasma bupivacaine levels, it is known that halothane anesthesia decreases splanchnic blood flow,[8] which would tend to slow the rate of metabolism by the liver and prolong blood levels of local anesthetics. In addition, general anesthesia has been shown to prolong the blood levels of orally administered lidocaine in patients undergoing laparoscopy.[9]

We conclude that intercostal blocks with bupivacaine-epinephrine solution are more likely to produce systemic toxicity or hypotension, or both, than other types of peripheral nerve blocks. In addition, the presence of congestive heart failure and a general anesthetic may enhance the possibility of reaching toxic levels of local anesthetic. We urge caution in using bupivacaine-epinephrine solution for intercostal nerve blocks in patients during general anesthesia.

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Nerve Block of the Penis for Postoperative Pain Relief in Children

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SURGICAL procedures such as circumcision and correction of hypospadias are followed by severe pain, which may give rise to restlessness and agitation during the postoperative period. Pain associated with penile surgery may also lead the pediatric patient to manipulate the site of surgery, occasionally causing postoperative hemorrhage or infection.[1]

It was observed that narcotics such as meperidine in the usual dose of 1 mg/kg IM produced slight pain relief with minimal change of behavior in children during the immediate postcircumcision period, and hence more effective analgesic methods remained to be found. Caudal block has been described and found to be an easy and satisfactory method of complete pain relief in such cases.[2-4] However, the possibility of complications[5] and related medico-legal risks limit its use.

Block of dorsal nerves of the penis[6,7] can provide postcircumcision pain relief similar to that obtained from caudal analgesia without the possibility of serious complications. This is a report of our experience with an alternative to IM narcotics or caudal anesthesia for postoperative analgesia following penile surgery in children.

ANATOMY[8,9]

There are two dorsal nerves of the penis: the right and the left. Each arises from the pudendal nerve, runs along the ischial ramus, then along the inferior ramus of the pubis, and emerges from the pelvis through the lateral part of the gap between the corpus cavernosum and the inferior pubic ligament.

In the penis, the nerve lies deep to the penile Buck's fascia, lateral to the dorsal

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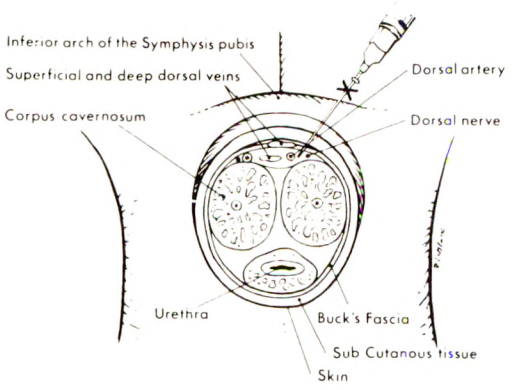


FIGURE. Cross-section of base of penis with needle in place for block of dorsal nerves

artery of the penis. The dorsal nerves of the penis carry sensory innervation from the glans and from the skin covering most of the shaft.

TECHNIC

The dorsal nerves of the penis can be blocked as they pass from the pelvis to the penis.

With the patient in the dorsal position, the skin over the symphysis pubis and the base of the penis is cleansed with antiseptic solution. The inferior border of the symphysis pubis is identified and a mark is made at that level 1 cm from the midline. A 23-gauge ¾-inch needle (to which is fixed a 5-ml syringe containing local anesthetic solution) is introduced through the mark and directed toward the midline at an angle of 30° to the skin and slightly caudad. As the needle advances, it pierces the skin, the subcutaneous tissue, and the penile fascia (figure); the latter sometimes causes a noticeable click. Once the needle has pierced the fascia, which is about 4 to 6 mm deep, we aspirate for blood. If aspiration is negative, the local anesthetic is injected. If blood is aspirated, the needle is relocated. The injection is made on one side only since both nerves lie in the same fascial plane (no midline separation) (figure). A discrete swelling at the base of the penis as the local anesthetic is injected confirms the position of the needle deep to the fascia.

While we were carrying out this study, Bacon[10] described a different technic for block of the dorsal nerves of the penis. With the abducted index and middle fingers of the left hand placed to palpate the lower border of the symphysis pubis, he inserts the needle between the two fingers vertical to the skin and advances until bony contact; he then redirects the needle to pass just inferior to the lower border of the symphysis pubis. The anesthetic solution is injected once the needle is judged to be midway between the lower border of the arch of the symphysis pubis and the root of the penis.

Since the dorsal veins lie in the middle line, we presume that the risk of transfixing them and subsequent hematoma formation may be higher with the midline approach described by Bacon than with the lateral approach we used.

METHODS

Seventy children, ASA physical status class 1, scheduled for circumcision (66 cases) and correction of hypospadias (4 cases were the subjects of this study. The patients were divided in two groups: group 1 (patients in whom nerve block of the penis was performed)—50 patients, and group 2 (patients in whom nerve block of the penis was not performed)—20 patients. Ages ranged from 4 months to 8 years. Sixty-five of the children were outpatients (table 1). This study was approved by the Research and Academic Committee of the Department of Anesthesia of our institution; written consent was obtained from a parent of each child.

Preanesthetic medication consisted of meperidine 1 mg/kg, hydroxyzine 1 mg/kg, and atropine 0.01 mg/kg IM 1 hour before anesthesia, in 62 patients.

Anesthesia was induced either IV using thiopental 5 mg/kg or by inhalation using O_2-N_2O and increasing concentrations of halothane. Maintenance was accomplished with N_2O-halothane (F_{IO_2} = 0.30), using a mask and Jackson-Rees modified T-piece circuit. In group 1 patients, once the vital signs were stable, the dorsal nerves of the penis were blocked as described previously, using plain bupivacaine 0.25%. The volume injected varied according to the age and weight of the patient. Thereafter the concentration of halothane was decreased to the minimum ($\leq 0.5\%$) required to main-

TABLE 1
Patients Studied

Group	No.	Age (years) <1	1-5	>5	Hospitalization Yes	No	Premedication Yes	No
1	50	12	28	10	5	45	42	8
2	20	8	8	4	0	20	20	0

tain a quiet, still patient. In group 2, there was no nerve block and the inspiratory concentration of halothane had to be maintained between 1.5 and 2%.

The block was judged to be satisfactory when there was no response to the surgical stimulus.

During the procedure, a slow IV infusion was maintained and the heart rate and rhythm and arterial blood pressure were recorded. In addition, body temperature was monitored in all patients aged 1 year or less. Each patient's behavior during recovery was observed, and the time elapsed before analgesics were administered was recorded. Agitated patients received meperidine 1 mg/kg IM, and their behavior was re-evaluated 30 minutes later.

RESULTS

The dosages of bupivacaine used are shown in table 2. The dosages used were below the maximum dosages recommended by the manufacturer.

Table 3 compares the incidence of agitation and the effects of narcotics in both groups. In group 1, only 4% of the patients were agitated and their postoperative behavior was not changed by narcotic administration. In group 2, 90% of the patients were agitated and meperidine administration was effective as a method of pain relief, as indicated by patient agitation, in only 8 out of 20 patients.

Table 4 shows the success and failure rates of the blocks. The block failed in 4% of the cases. In all cases where the block was successful, we observed that $\leq$0.5% halothane in N_2O-O_2 was all that was required to provide a quiet, still patient during surgery with no response to surgical stimulus. All other patients, including group 2 patients, required $\geq$1.5% halothane for the same purposes.

TABLE 2
Volume and Dose of Local Anesthetic

Bupivacaine 0.25%	
Volume (ml)	Dose mg/kg (SE)
1-4	0.54 (0.01)

TABLE 3
Comparison of the Incidence of Postoperative Agitation and the Effect of Meperidine

		Agitated	
Group	No.	15 min. postoperatively	30 min. after meperidine
1	50	2	2
2	20	18	12

TABLE 4
Comparison of Satisfactory and Unsatisfactory Block

	No.	Recovery	Time Before 1st Dose of Analgesic
Satisfactory	48	Quiet	> 6 hours
Unsatisfactory	2	Agitated	<15 minutes

In the patients where the block was unsuccessful, analgesics were required within 15 minutes postoperatively.

Outpatients with successful blocks required no postoperative analgesics nor repetition of the block during the time of their stay in the hospital—a minimum of 6 hours. Four of the hospitalized patients underwent correction of hypospadias and none of these required any analgesia during the first 48 hours postoperatively. The remaining hospitalized patient (who had undergone circumcision), discharged the next day, required no postoperative analgesia. The block was successful in all hospitalized patients.

In no case were the dorsal veins of the penis pierced nor was there hematoma formation.

DISCUSSION

We found that block of the dorsal nerves of the penis is a very simple, easy, and satisfactory method of pain relief following circumcision and correction of hypospadias.

The dosages of local anesthetic used were effective and well below toxic levels. The absence of side effects from local anesthetics and the higher success rate from this block make this method of analgesia for pain from penile surgery in children preferable to the use of narcotics, especially in outpatients.

We have used caudal anesthesia to provide pain relief from penile surgery in children and have reported satisfactory results. Our results have been published elsewhere.[4] Although there were no neurological complications in our series, these have been reported by others.[5] The absence of this remote possibility with its medicolegal consequence and the equally satisfactory results make the block of the dorsal nerves of the

penis superior to caudal anesthesia for postoperative pain relief after penile surgery.

Although we felt that successful block was adequate for the performance of the surgery, we added just enough general anesthesia to maintain a quiet, still child during the procedure. We feel that general anesthesia is safer than movement of the child during the operation and is safer than other technics serving the same purposes, such as the use of restraints or heavy sedation.

Although our experience of this block is limited to children, we have no reason not to expect equally satisfactory results in adults. There is an anecdotal report claiming such success.[7] In such cases, general anesthesia could obviously be omitted with a willing and cooperative adult.

In summary, using 0.25% bupivacaine we blocked the dorsal nerves of the penis for postoperative pain control after circumcision and correction of hypospadias in children. The block was shown to be easy to perform and successful in 96% of the 50 patients in whom it was done; successful block was associated with quiet recovery and pain relief superior to that produced by meperidine 1 mg/kg IM. The doses of local anesthetic used were well below toxic levels. The absence of complications and the simplicity of the block made it superior to other methods of analgesia used for the same purposes.

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Cardiac Arrest with Electromechanical Dissociation

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THIS report concerns a 33-year-old man who suffered cardiac arrest with electromechanical dissociation* during anesthesia for emergency pericardotomy.

CASE REPORT

The patient, in chronic renal failure, received a renal transplant in 1975. The donor kidney was rejected and removed in February 1976. He was readmitted in September 1976 with a diagnosis of acute pericarditis. At that time, there was a pericardial friction rub but no evidence of effusion. A week later, he became hypotensive during routine hemodialysis. After dialysis, his blood pressure was 118/70 mm Hg, pulse 96/min, and respirations 18/min. There was marked jugular venous distention without paradoxical filling during inspiration. The liver was pal-

*Electrocardiogram showing electrical conduction of beats in the absence of effective contraction

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pable 8 cm below the costal margin. There were basal rales in the lungs. He weighed 85 kg, 7 kg over his usual weight. Electrocardiogram showed regular sinus rhythm with left bundle branch block. Chest x-ray showed marked enlargement of the cardiac silhouette, probably due to pericardial effusion. Relevant blood values were hemoglobin 7.1 gm/100 ml, hematocrit 23%, potassium 5.6 mEq/L, urea nitrogen 79 mg%, creatinine 11.7 mg%, and glucose 66 mg%.

Emergency pericardotomy was recommended. This was preceded by pericardiocentesis. There was marked symptomatic improvement following removal of 1100 ml of serosanguinous fluid during the next 16 hours.

The patient was premedicated with diphenhydramine 100 mg and meperidine 50 mg IM and arrived in the operating room rather undersedated. At this time, his blood pressure was 100/64 mm Hg and pulse rate 100/min. It was decided to use neuroleptanesthesia with diazepam 5 mg followed by incremental doses of meperidine to a total of 70 mg IV. Anesthesia was induced with N_2O and O_2 and he was given 5 mg tubocurarine (to prevent fasciculations) followed by succinylcholine 100 mg. He was ventilated with 100% O_2 and the trachea was intubated. High airway resistance was noted on manual ventilation and the position of the tube was confirmed by laryngoscopy and bilateral auscultation of the chest. An Air-Shields anesthesia ventilator was set to deliver a mixture of 70% N_2O and 30% O_2 with a tidal volume of 700 ml at a frequency of 12/min. The patient was positioned for left thoracotomy in the semilateral position. There was no change in vital signs or ECG until the skin was being prepared for surgery, when the ECG monitor showed a bradycardia of 60/min with absent P waves (junctional rhythm). This represented a considerable change of heart rate, and atropine 0.4 mg IV was administered. The heart continued to slow and an isoproterenol infusion (800 μg/ml) was started. The ECG tracing reverted to normal rate and sinus rhythm but the blood pressure became unrecordable and the carotid pulse disappeared.

Cardiac arrest was diagnosed, and in view of the patient's position on the table, and readiness for surgery, it was decided to proceed to internal cardiac massage. Due to adhesions, there was a brief delay in reaching the heart, which was at complete standstill, despite normal complexes on the ECG monitor. There were about 500 ml fluid in the pericardial sac and 1000 ml in the pleural cavity. The heart was grossly enlarged and its surface covered with a coarse red fibrinous exudate. The pupils were now widely dilated. Following internal cardiac massage spontaneous beats recommenced, and a normal blood pressure was maintained with an infusion of dopamine (800 μg/ml). The pupils contracted, and the operation (pericardotomy) was quickly concluded. He received 66 mEq sodium bicarbonate; a central line (CVP) inserted via the left internal jugular vein showed a pressure of 10 cm H_2O. (Subsequent x-ray showed the catheter tip to be in the right internal jugular vein, outside the thoracic cavity.) The patient was taken to the recovery room, where the CVP line was replaced by a thermodilution Swan-Ganz type catheter, and an axillary intra-arterial catheter was inserted. Pulmonary arterial pressure was 65/25 torr; pulmonary capillary wedge pressure ranged from 25 to 32 torr. On F_{IO_2} of 0.6, arterial blood gases were pH 7.20, P_{CO_2} 47.8 torr, P_{O_2} 71.8 torr, and base deficit was 9.5 mEq/L. Chest x-ray showed marked congestive changes indicative of cardiac failure, with bilateral pleural effusions.

He had several further episodes of cardiac arrest (featuring bradyarrhythmias), which were successfully treated with external cardiac massage. The next morning, following another arrest and resuscitation, his pulmonary artery pressures were 28/16 torr, wedge pressure 8 torr, and cardiac output 7.2 to 8.2 L/min. He responded to volume infusion. It was thought that the hemodynamic changes might have been due to fluid shift from the circulation. He was maintained on artificial ventilation and required muscle paralysis with pancuronium for synchronization with the ventilator. He remained in coma for 3 weeks, responding only to painful stimuli. A tracheostomy was performed and gradually he was weaned off the ventilator and recovered his preoperative mental state, although emotionally remaining withdrawn. He had residual weakness of his legs and flexion deformities of the wrist from his previous decorticate posture and he lost a great deal of weight. He was discharged from the hospital to a nursing home. He was maintained on hemodialysis and on occasional peritoneal dialysis. He had an unexpected cardiac arrest and died 8 months after the initial episode. There was no autopsy.

DISCUSSION

Before surgery, the patient had acceptable vital signs, despite obvious pallor. It was known that he was in chronic renal failure, and the hazards of anemia, pericarditis, hyperkalemia, and uremia were appreciated, but the severity of his condition was underestimated.

Induction—In order to avoid technics which could result in a rapid disturbance of hemodynamic equilibrium, neuroleptanesthesia was chosen.[1] Diazepam rather than droperidol was used, as its duration of action is shorter, and it has no alpha blocking action. In the presence of cardiac tamponade, it is important to avoid drugs such as thiopental, which may cause a fall in peripheral resistance at a time when compensatory increase in cardiac output cannot take place.[2] The use of a muscle relaxant for intubation may be disputed, as controlled ventilation can aggravate the effects of cardiac tamponade. Alternative recommendations are (a) intubation under topical anesthesia, followed by inhalation anesthesia until the pleura is open,[3] or (b) sternal incision under local anesthesia, and induction of general anesthesia with thiopental, succinylcholine, and inhalation anesthesia after relief of tamponade.[4] As the pericardium had been drained during the 16 hours prior to operation, it was considered that pericardial tamponade was no longer likely. In fact, there were no overt changes in circulatory vital signs associated with institution of controlled ventilation.

Succinylcholine—There is a rise in serum potassium following injection of succinylcholine which is of the order of 0.5 mEq/L in both normal and uremic patients.[5] The severe rise seen in trauma and burns is not seen in uremia, although there are reported cases of hyperkalemic cardiac arrest following succinylcholine in uremic patients. Some would consider succinylcholine contraindicated in uremia.[6,7] Other authors believe it to be safe, provided the initial serum potassium is not above 5.5 mEq/L.[8] In our patient, at no time during surgery did the ECG show peaked T waves, wide QRS complexes, or ventricular arrhythmias which might have indicated hyperkalemia. It is, therefore, our opinion that succinylcholine-induced hyperkalemia did not precipitate cardiac arrest in this man. Unfortunately, a blood sample was not obtained during the arrest for determination of serum potassium levels.

Cardiac Impairment—At the time of induction of anesthesia, it was not realized that the patient was about 7 kg above his usual weight; clearly, he was fluid overloaded. Echocardiogram one week prior to surgery showed cardiac enlargement without effusion. In view of his previous instability during hemodialysis, and the relative urgency of the operation, it was not possible to dialyze him immediately before surgery. The large cardiac shadow seen on the previous night's chest x-ray had been interpreted as pericardial effusion and this was consistent with jugular venous distention and an enlarged liver. However, these signs are also compatible with congestive cardiac failure. The high pulmonary capillary wedge pressure immediately after surgery and the large heart seen at thoracotomy also confirm that the patient was anesthetized when he was in congestive failure. Difficulty in ventilation and a fall in lung compliance, giving the feeling of "stiff lungs," are consistent with left heart failure and pulmonary edema. Postoperative chest x-ray confirmed this. The chest film from the previous night was somewhat overpenetrated and could have obscured signs of pulmonary congestion. He had improved symptomatically after drainage of his effusion, and the volume of residual fluid in the pericardium at thoracotomy did not suggest that arrest was caused by pericardial tamponade. Twenty minutes following a smooth induction of anesthesia, the first danger sign was the occurrence of bradycardia. Since he had not received preoperative atropine, and because succinylcholine can exert a cholinergic effect on the heart, the use of IV atropine was reasonable. However, in the presence of ventilatory difficulty, hypoxia should have been suspected, and the inspired O_2 concentration increased. With a hemoglobin level of 7.1 gm/100 ml, O_2 content at 100% saturation could only be 9.5 ml/100 ml. Normal myocardial O_2 extraction is stated to be 11 ml/100 ml.[9] Even moderate hypoxia would have reduced the O_2 content of his coronary arterial blood to critical levels.

Isoproterenol—The onset of hypotension coincided with the infusion of isoproterenol. His heart arrested even though normal electrical activity continued at an improved rate. Isoproterenol, a beta adrenergic agent, causes peripheral vasodilatation, thus contributing to hypotension. It is also a powerful cardiac stimulant, affecting rate rather than stroke volume,[10] resulting in increased cardiac work and O_2 consumption. The increase in myocardial work and O_2 require-

ment exceed the improvement in myocardial perfusion and oxygenation.[11] By increasing O_2 consumption in the presence of a limited supply, it may be that the infusion of isoproterenol was the final precipitating factor in producing cardiac arrest. Cardiac standstill rather than ventricular fibrillation suggest myocardial hypoxia rather than hyperirritability.

In summary, it appears that the mechanism of arrest was not so much through the wrong choice of agents or technics of anesthesia, but failure to appreciate the degree of cardiac decompensation and fluid overload. In retrospect, it seems that the operation should have been delayed to give time for peritoneal dialysis, meanwhile relying on pericardial drainage to prevent tamponade.[12] Unexplained bradycardia should alert the anesthesiologist to the possibility of hypoxia, and this should be excluded before resorting to drugs for its symptomatic treatment. Electrocardiographic monitoring is clearly inadequate for the detection of changes in cardiac performance; in our case ECG complexes were normal in the presence of cardiac standstill observed at thoracotomy. Intra-arterial pressure monitoring, blood gas analyses, and a CVP line are strongly recommended in handling such poor-risk patients.

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Cardiac Arrest Following Pneumonectomy and Pericardiotomy

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HERNIATION of the heart through a pericardial defect is a recognized complication of pneumonectomy requiring pericardiotomy.[1,2] Since this can occur in the immediate postoperative period,[1-3] the anesthesiologist must be aware of the possibility and be able to make the diagnosis. The following case illustrates this point.

CASE REPORT

A 33-year-old female with a bronchoscopic diagnosis of squamous-cell carcinoma of the

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lung and a negative mediastinoscopy was scheduled for a right pneumonectomy.

Preoperative evaluation, including pulmonary function studies, was within normal limits. Chest x-ray revealed a right hilar mass and a right upper lobe lesion. In the operating room the left radial artery was cannulated to monitor arterial blood gases. A central venous pressure line was not judged to be necessary and was not inserted. Anesthesia was induced with thiopental 300 mg and maintained with 0.5 to 1% halothane, pancuronium 4 mg, and 50:50 N_2O:O_2. With the right lung retracted, Pao_2 ranged from 170 to 140 torr. Occasional transient ventricular extrasystoles were associated with retraction of the hilum. On one occasion, when these extrasystoles became multifocal, lidocaine 50 mg was given IV. With the exception of these episodes of dysrhythmia, the anesthetic was uneventful. It was necessary for the surgeon to open the right pericardium to complete the pneumonectomy. A 4-cm defect was made, and several sutures were placed to close it to less than 3 cm.

At the conclusion of the procedure, spontaneous respiration resumed, and neostigmine 1.25 mg and atropine 0.5 mg were given to antagonize the residual neuromuscular block. The patient's vital capacity was judged to be satisfactory since she generated an adequate cough. She was extubated after receiving 100% O_2 for about 5 minutes. She was then taken to the recovery room. The transit time was about 90 to 120 seconds. On arrival, she appeared cyanotic and palpable pulses had disappeared. She was ventilated by bag and mask and then reintubated. Simultaneously, external cardiac massage was begun. Almost immediately a palpable pulse returned, and blood pressure was recorded in the range of 80-100/40-60 mm Hg with a sinus rhythm of 90 to 100 beats/min. The patient was reactive but still had cyanosis of the head, neck, upper extremities, and upper thorax. A portable chest x-ray was immediately obtained and showed the heart to be occupying the right pleural cavity (fig 1).

The patient was immediately returned to the operating room. Ketamine 100 mg, pancuronium 2 mg, and 50:50 N_2O:O_2 were given and the right chest was reopened. The heart was found to have herniated through the pericardiotomy opening and to have rotated 180° posteriorly to anteriorly so that the left ventricle was presenting anteriorly

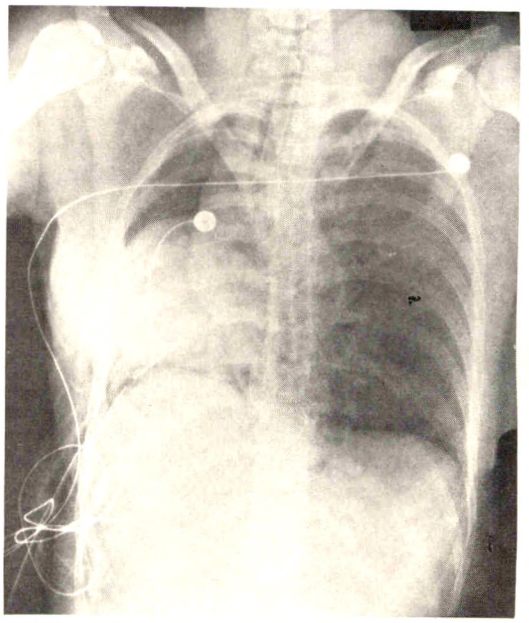


FIG 1. Portable chest x-ray taken in recovery room shows heart filling the right pleural space.

in the right pleural space. The heart was reduced to its appropriate position. The blood pressure increased to 120/80 mm Hg, the heart rate slowed to 80 beats/min, and the cyanosis rapidly cleared. The pericardial defect was closed with a Dacron patch. The patient was extubated the next morning and made an uneventful recovery. Figure 2 shows the patient's chest x-ray after extubation.

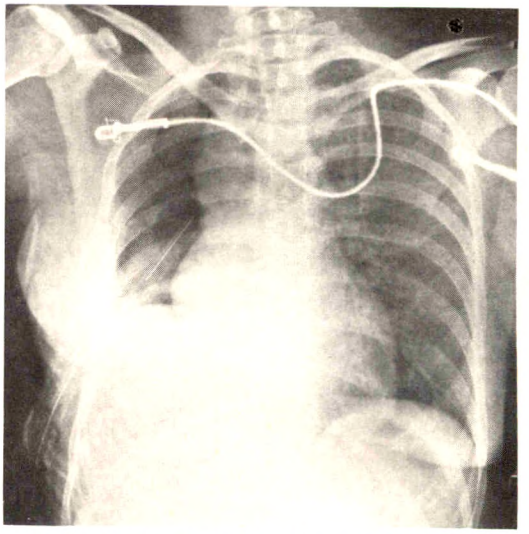


FIG 2. Chest x-ray taken after extubation shows the normal appearance of the heart after a right pneumonectomy.

DISCUSSION

The dramatic change in this patient's condition from reactive with spontaneous respirations to a cardiac and respiratory arrest indicated a catastrophic event occurred. With the resumption of circulation in the presence of artificial ventilation, the cyanosis of the upper body suggested superior vena cava obstruction. This was confirmed at reoperation. Previous reports indicate that if the heart herniates through an unclosed pericardiotomy, it usually does so in the immediate postoperative period[1-3] although it may occur many hours postoperatively.[1] The outcome has often been fatal due to damage occurring to the heart, which can become strangulated in the pericardial defect.[1,2] On occasion the diagnosis has been made only at autopsy.[2] The favorable outcome in this case as in others[3] is the result of prompt diagnosis and surgical reduction.

Yacoub[1] states that the precipitating factors in addition to the size and site of the defect in the pericardium include (1) suction applied to pleural drainage tubes; (2) rolling the patient to the operative side; (3) violent bouts of coughing; and (4) hyperinflation of the remaining lung. Our patient did cough several times prior to extubation and this possibly could have caused the herniation.

In summary, a case of cardiac arrest following pneumonectomy requiring pericardiotomy is reported. The anesthesiologist is likely to see this complication since most previously reported cases have occurred in the immediate recovery period. In the event of inability to resuscitate a patient whose pericardium has been opened, a chest x-ray is indicated, and it would be wise to reopen the chest to rule out herniation of the heart before ceasing resuscitation efforts.

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Anesthetic Management of a Patient with Hereditary Fructose-1, 6-Diphosphatase Deficiency

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HEREDITARY fructose-1,6-diphosphatase (FDPase) deficiency is a rare and little understood genetic disorder first described by Baker and Winegrad in 1970.[1] The clinical course of this disorder is characterized by (1) recurrent episodes of hypoglycemia precipitated by stress, such as acute infections, and by ingestion of fructose; and (2) severe metabolic acidosis evidenced by hyperventilation. Hepatomegaly and muscular hypotonia are frequent, and fatty changes of the liver have been seen without exception.[1-10] Mental development and growth remain normal despite fructose intake.[11] Up to 1977, 11 patients with FDPase deficiency from 3 European coun-

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tries and from the United States have been reported.

We present the case of a patient with hereditary FDPase deficiency undergoing open liver biopsy. We have found no prior report on the anesthetic management of a patient with this disorder.

REPORT OF A CASE

A 23-month-old boy was scheduled for open liver biopsy. He was the 3rd child of healthy, consanguineous parents. Two other siblings were healthy. His first hospitalization for a disturbance of consciousness occurred at 7 months of age following persistent diarrhea and vomiting. Laboratory studies revealed hypoglycemia (56 mg/100 ml) and ketonuria. He responded well to therapy with IV administration of glucose. At 10 months of age the patient was admitted to his local community hospital following bronchitis with slight fever and diarrhea with a blood glucose level of 45 mg/100 ml. At 17 months of age he developed loss of consciousness following a short convulsive episode. His blood glucose was 6 mg/100 ml and large amounts of urinary ketones (+++) were present. He improved rapidly after treatment with IV glucose and sodium bicarbonate. Three months later, he was referred to Tohoku University Hospital for further evaluation and treatment.

His height was 83 cm, weight 11.3 kg, and hemoglobin 13.0 g/100 ml. The ECG, chest x-ray, urinalysis, and serum electrolytes were within normal limits. The liver was palpable 4 cm below the right costal margin. Laboratory values were as follows: blood glucose 34 to 86 mg/100 ml (normal range in our institution 60 to 100 mg/100 ml); lactate 19.5 mg/100 ml (normal 5.2 to 16.6 mg/100 ml); pyruvate 0.85 mg/100 ml (normal 0.5 to 1.2 mg/100 ml); uric acid 4.6 mg/100 ml (normal 2.9 to 6.5 mg/100 ml); free fatty acids 0.5 mEq/L (normal 0.2 to 0.6 mEq/L); triglycerides 63 mg/100 ml (normal 65 to 120 mg/100 ml); cholesterol 170 mg/100 ml (normal 132 to 198 mg/100 ml). Blood lactate dehydrogenase and alkaline phosphatase levels were moderately elevated; SGOT and SGPT were normal. Both alanine (0.5 g/kg) and fructose (1 g/kg) administration orally after an overnight fast caused a decrease in blood glucose levels and an increase in lactate concentration. Twelve hours after an oral ketogenic diet (700 Cal/day/m^2), hypoglycemia occurred and glucagon (0.03 mg/kg) administration IM failed to increase blood glucose levels. On the other hand, an oral glucose (2 g/kg) loading after fasting for 12 hours caused an increase in blood glucose with a slight decrease in blood lactate. Because of these findings, the patient was suspected of having hereditary fructose intolerance.[11] To confirm the diagnosis, he was scheduled to undergo laparotomy and liver biopsy.

Premedication consisted of meperidine (10 mg) and atropine (0.1 mg) IM approximately an hour before induction of anesthesia. Thirty minutes after premedication, an IV infusion of 5% glucose was started. Upon arrival in the operating room, blood glucose was 30 mg/100 ml.

The trachea was intubated after induction of anesthesia with halothane (0.5 to 3.0%)-N_2O-O_2 (3:1.5 L/min) by mask. Anesthesia was then maintained with halothane (1.5%)-N_2O-O_2 (3:1.5 L/min) and alcuronium (2 mg). The patient was manually ventilated throughout the 40-minute open liver biopsy. Monitoring included a precordial stethoscope, a blood-pressure cuff, a cardioscope, and an esophageal thermometer. Five minutes after intubation, blood gas determinations confirmed a severe metabolic acidosis, with pH of 7.23, $Paco_2$ of 39 torr, Pao_2 of 189 torr, and BE of −10.2 mEq/L. Sodium bicarbonate 16.7 mEq (20 ml of 7% solution) was administered IV. Blood glucose level during the operation gradually increased to 90 mg/100 ml.

At the end of the operation, atropine (0.4 mg) and neostigmine (0.8 mg) were used to reverse the muscle relaxant. Five minutes after reversal, arterial blood gases while the infant was breathing 100% O_2 showed pH 7.35, $Paco_2$ 32 torr, Pao_2 340 torr, and BE −6.7 mEq/L. His blood glucose was 90 mg/100 ml, and esophageal temperature was 36.9 C. The infant responded to verbal commands and was extubated in the operating room. He received 100 ml of 5% glucose during anesthesia.

Vital signs remained stable for an 85-minute stay in the recovery room. Sodium bicarbonate (8.3 mEq) was given twice IV. Arterial blood gases while the infant was breathing enriched O_2 via a facemask were pH 7.38, $Paco_2$ 32 torr, Pao_2 100 torr, and BE −5.2 mEq/L. Blood glucose was 74 mg/100 ml. He was awake and could follow verbal commands and was then transferred to the ward. His postoperative course was

uneventful and he was discharged 30 days postoperatively. Enzyme assays of a liver tissue using the method of Edgar et al[12] revealed that FDPase activity was undetectable, while that of a control liver obtained from a child with glycogen storage disease, type 1, was 15.8 μmoles/g wet liver/min.

DISCUSSION

FDPase is 1 of 4 rate-limiting enzymes unique to hepatic gluconeogenesis; it is necessary for the conversion of fructose-1,6-diphosphate into fructose-6-phosphate and inorganic phosphate.[13] With a deficiency of this enzyme, the liver is unable to transform fructose, lactate, glycerol, and amino acids such as alanine to glucose. During fasting, liver glycogen decreases and blood glucose levels are maintained primarily by the conversion of alanine to glucose. A deficiency of FDPase can be expected to cause an elevation of plasma alanine, which results from both increased peripheral production and decreased hepatic uptake.[14] When liver glycogen stores have been depleted by a prolonged fast or a ketogenic diet, hypoglycemia and lactic acidosis result. Furthermore, in the absence of FDPase, accumulation of fructose-1,6-diphosphate can lead to promotion of pyruvate formation from phosphoenolpyruvate, resulting in still more severe lactic acidosis since it has been shown that FDPase activates pyruvate kinase allosterically.[15]

On the other hand, the mechanism of hypoglycemia which is induced by fructose or glycerol in FDPase deficiency is not clear. Melancon et al[6] reported that IM administration of epinephrine failed to raise blood glucose concentrations after a fructose load. They suggested that the accumulation of fructose-1,6-diphosphate directly inhibits glucose release from the liver.

In the case reported here, we had inadequate preoperative assessment and preparation, as evidenced by a blood glucose of 30 mg/100 ml, and BE of −10.2 mEq/L before and shortly after induction of anesthesia. Profound hypoglycemia and hyperlactic acidemia are precipitated by oral fructose and by prolonged fasting in infants with complete deficiency of FDPase.[1,3,6,7,9] Therefore, the metabolic acidosis and hypoglycemia experienced in the operating room in this patient could probably have been avoided by 2 steps. First, fructose must be totally eliminated from the diet for 24 to 48 hours when this diagnosis is suspected. Secondly, administration of a sufficient amount of IV glucose during the preoperative fasting period should be routine in this disease. Blood lactate measurement, if possible, would reflect utilization of IV glucose in the glycolytic pathway, since an oral glucose loading after overnight fast in this patient caused an increase in blood glucose with a decrease in blood lactate level. Based upon our experience, an arterial catheter for periodic measurement of blood gases and blood glucose levels would appear indicated.

It has been reported that sorbitol administered IV induces hypoglycemia and lactic acidosis identical with those seen after IV fructose administration in patients with FDPase deficiency, since sorbitol is first converted to fructose by sorbitol dehydrogenase.[14] Therefore, both fructose and sorbitol IV solutions are dangerous and are contraindicated in this disease. Furthermore, when lactic acidosis exists, lactated Ringer's solution may also be contraindicated, since lactate may not be metabolized and can lead to more profound lactic acidosis.[7]

Anesthetic management primarily involves concern with prevention of an augmentation of the already present tendency toward metabolic acidosis. The duration of anesthesia in our case was relatively short, and blood loss was 20 ml. However, long duration of anesthesia, blood transfusion, and hypothermia would produce significant metabolic acidosis. Metabolic acidosis should be corrected with sodium bicarbonate according to the measured BE, not only during anesthesia, but also during the preanesthetic period.

Halothane-N_2O anesthesia was selected. Halothane causes minimal changes in blood glucose,[16] while fluroxene, diethyl ether, and cyclopropane cause hyperglycemia via catecholamine-stimulated gluconeogenesis. Since IM glucagon after 16 hours fast failed to cause an increase in blood glucose in this disease,[6] catecholamine-induced glucose mobilization by these anesthetics would not be expected unless blood glucose levels have been maintained within a normal range. Thus, these anesthetics may offer little advantage over halothane in this respect. Regardless of the anesthetic selected and the amounts of IV glucose administered, blood glucose levels should be frequently measured throughout the course of anesthesia and surgery.

Finally, blood glucose and blood gases

should continue to be monitored in the postoperative period until therapeutic dietary regimens may be instituted. Dietary restriction of fructose, sucrose, sorbitol, and glycerol appears to be useful in the management of this disease.[6,10]

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Intravenous Lidocaine Controls Extubation Laryngospasm in Children

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LARYNGOSPASM is a serious complication which may be seen following extubation of children under "light" anesthesia. During laryngospasm, either the true vocal cords or the true and false cords become opposed in the midline and close the glottis.[1] The present report shows that IV injection of lidocaine 2 mg/kg of body weight can be safely used to prevent or control extubation laryngospasm.

METHOD

Forty children undergoing tonsillectomy were studied. Their ages ranged from 3 to 6 years, and body weights from 13 to 23 kg. All patients were premedicated 45 to 60 minutes prior to surgery by IM injections of meperidine 2 mg/kg, pentobarbital 4 mg/kg, and atropine 0.3 to 0.6 mg. Anesthesia was induced by halothane 2 to 4% in 5 L of O_2, using the T-piece system. All children

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were intubated using orotracheal tubes of internal diameters equal to $\frac{\text{age}}{3} + 3.5$ mm. Anesthesia was maintained with halothane 1 to 2% in O_2. Halothane was discontinued 5 to 10 minutes before the end of surgery, which lasted 30 to 60 minutes. The ECG was monitored throughout the procedure in all patients.

In 20 children, a bolus of 2% lidocaine (2 mg/kg) was injected IV one minute prior to extubation; in the other 20 children, extubation was carried out without prior injection of lidocaine. The incidence of laryngospasm following extubation was observed in both groups.

RESULTS

In the group of children given prophylactic lidocaine (2 mg/kg), no laryngospasm followed extubation. On the other hand, severe laryngospasm followed extubation in 4 children of the control group. In these 4 children, the subsequent IV injection of lidocaine (2 mg/kg) controlled the spasm within 30 to 90 seconds.

No serious systemic effects followed the IV injection of lidocaine, whether it was used to prevent or to control extubation laryngospasm. Moderate bradycardia was observed in 1 child, and transient respiratory depression occurred in 2 other children. Recovery of all patients was uneventful.

DISCUSSION

Intravenous lidocaine has been used in adult patients to prevent "bucking" during extubation under "light" anesthesia.[2] An IV bolus of 2% lidocaine, 2 mg/kg, was necessary to provide such protection. This dose resulted in a lidocaine plasma level of over 3 μg/ml, which was maintained for less than 5 minutes.[2]

The present report shows that a similar dose of lidocaine can be successfully used in children, either to prevent or to control extubation laryngospasm. The mechanism by which lidocaine blocks the laryngospasm reflex arc may be a central interruption of the reflex pathway, or a direct peripheral action on the sensory or the motor nerve terminals. The technic is simple, effective, and can be safely employed in clinical anesthesia.

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Hydrohemothorax Following Percutaneous Internal Jugular Vein Cannulation Recognized by Intravenous Pyelography

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PERCUTANEOUS cannulation of the internal jugular vein has become an accepted technic for monitoring central venous pressures (CVP) or, via a Swan Ganz catheter, pulmonary artery pressures. The technic is not without hazard. Complications include mediastinal infiltration and hydrothorax.[1-3]

The present case report demonstrates failure to recognize the extravascular posi-

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tion of an internal jugular catheter when conventional procedures were relied upon.

REPORT OF A CASE

A 22-year-old woman was admitted from an outside hospital following an automobile accident in which two other occupants of her car were killed. She was unconscious, with an endotracheal tube in place; lactated Ringer's solution was being perfused through a peripheral vein in her right arm. Systolic blood pressure was 50 to 60 torr. Auscultation of her left chest demonstrated decreased air entry.

An attempt to cannulate the right internal jugular vein was abandoned when the catheter could not be threaded down the vessel. The catheter was not used but was left in place until a chest roentgenogram was obtained. This showed mild interstitial changes suggesting pulmonary contusion; the mediastinum was questionably wide but said to be within normal limits (fig 1). Peritoneal lavage and urinary catheterization yielded grossly blood-stained fluids. Following rapid transfusion, the patient was transferred to the operating room for exploratory laparotomy.

After induction of anesthesia, percutaneous left internal jugular catheterization was done without apparent difficulty with a 13-cm 16 G Angiocath(TM) (Deseret). After final positioning of the catheter and its connection with a manometer, blood was easily aspirated and fluctuation of the venous pressure with respiration was observed on the manometer. Central venous pressure (CVP) was 2 cm saline.

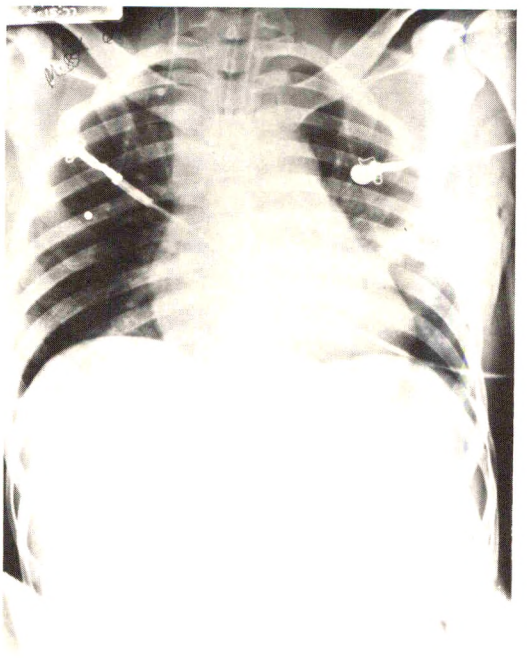


FIG 1. Chest roentgenogram taken shortly after cannulation of the right internal jugular vein was attempted. Patient had been injured in automobile accident.

A ruptured spleen was removed and a large retroperitoneal hematoma drained. Blood loss, replaced intraoperatively, was estimated to have been approximately four units. The patient's blood pressure ranged between 120/80 and 150/90 torr throughout the operation. The CVP line was used to infuse 5% dextrose in lactated Ringer's solution but was not used for blood transfusion. The CVP rose to 12 cm saline when the abdomen was closed at the end of the operation.

On admission to the intensive care unit, the patient's systolic blood pressure was 80 torr and her CVP 13 to 14 cm saline. In the ensuing 30 minutes, a complete blood cell count and sequential multiple assay computer (SMAC) (blood samples drawn from the CVP line), intravenous pyelography (IVP), and chest roentgenography were done in that order. For the IVP, Renografin-60,® 150 ml, was injected via the internal jugular vein catheter. Since there may have been cardiac contusion at the time of the accident and since blood volume seemed uncertain, a Swan-Ganz catheter was inserted via the right subclavian vein. The IVP results were then returned and showed extraperitoneal or thoracic dye in the left upper quadrant (fig 2). The chest roentgenogram (fig 3) confirmed a left tension hydrothorax, "the radiopaque fluid probably representing radiographic contrast medium." The left internal jugular CVP line could be seen passing behind the head of the clavicle on the left and terminating alongside the body of T4. The results of the SMAC were grossly abnormal: sodium, 128 mEq/L, potassium, 7.1 mEq/L, glucose, 1059 mg/dl, and protein, 1.1 gm/dl. The extravascular CVP cannula was removed and chest drainage begun. From the left side of the chest, 2300 ml of grossly blood-stained fluid (hematocrit 17%) was removed; while 350 ml of similar fluid was obtained from the right side. Subsequent chest roentgenogram (fig 4) showed relief of the tension hydrothorax and reduction in the size of the mediastinum. There was some increase in the inter-

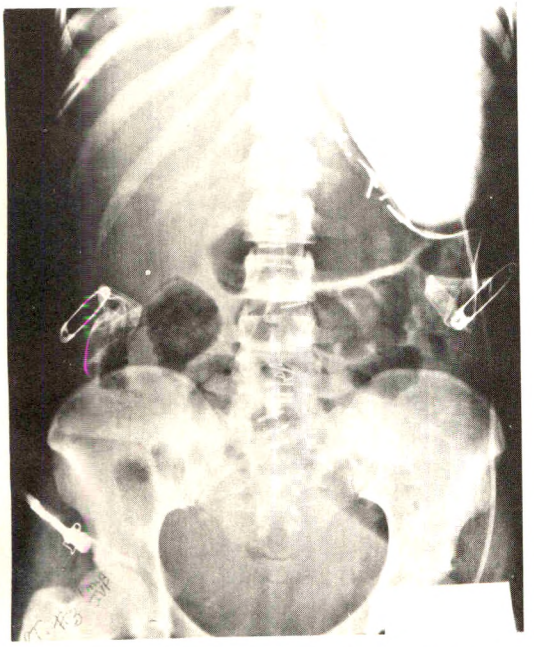


FIG 2. Intravenous pyelogram showing extravasation of the contrast medium extraperitoneally in the left upper abdominal quadrant and left thoracic cavity.

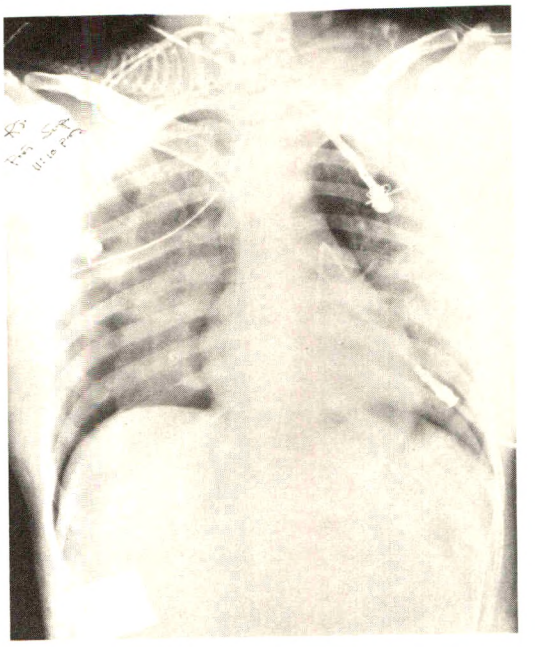


FIG 4. Chest roentgenogram taken after drainage of left and right thorax. Compare mediastinal width with that in fig 1.

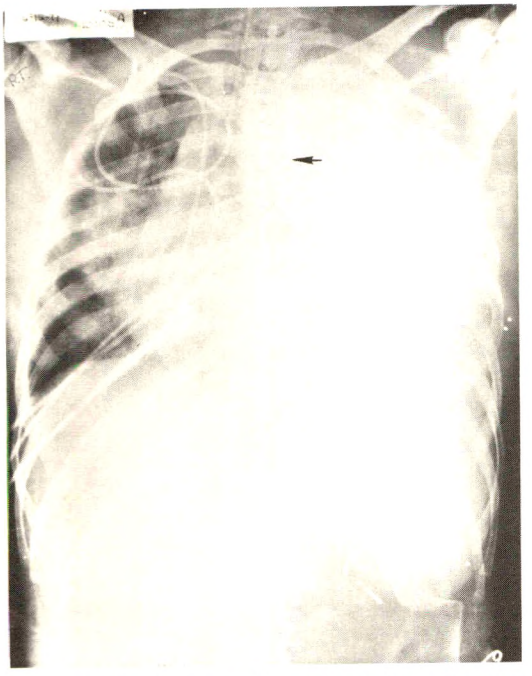


FIG 3. Roentgenographic confirmation of extravascular IVP dye. The left jugular catheter passes behind the left clavicular head and terminates (arrow) at the level of the body of T4. The superior vena cava can be identified by the course of the pulmonary artery catheter.

stitial changes in the left lung field noted previously.

It was concluded that the patient suffered mediastinal bleeding before admission as a result of the accident, and that the blood served to obscure the extravascular placement of the CVP line. No further bleeding occurred and the subsequent course was uneventful.

DISCUSSION

The accurate placement of central venous cannulae continues to vex the anesthetist, although the internal jugular approach appears to be more successful than other routes.[1-5] Not only must the tip be placed in the vicinity of the right atrium to give accurate pressure measurements,[4] but an intravascular position must be assured to prevent the serious complications of mediastinal infiltration and hemohydrothorax.[1-3]

Three tests are generally recommended to evaluate catheter placement. (1) With the catheter in the proper position, it should be possible to aspirate blood without difficulty.[1-2,5] (2) The saline level of the manometer should oscillate with the respiratory and cardiac cycles if the catheter is correctly placed.[6] However, this sign can be elicited when the catheter is outside the central ve-

nous system, resulting in the measurement of erroneously high pressures.[4] (3) Chest roentgenograms may reveal abnormal collections of air or fluid, suggesting a complication of catheter placement or extravascular position. Only injections of radiopaque contrast medium can guarantee IV positioning.

In the case described here, immediate chest roentgenography was impractical since the catheter was placed during a laparotomy. Easy aspiration of blood was possible both after insertion of the catheter and on two subsequent occasions, the last being immediately before injection of the IVP contrast medium. In addition, oscillations of the manometer were observed when the patient was ventilated. It was suggested that the latter sign may be found when the mediastinum is filled with blood or fluid. To test this hypothesis, the following experiment was made.

A 10-kg beagle was anesthetized in the dorsal position with pentobarbital (32.5 mg/kg) and ventilated through an endotracheal tube at 24 breaths per minute with a Harvard respiratory pump. The superior vena cava was cannulated via the right external jugular vein with a 13-cm 16 G Angiocath.(TM) A similar catheter was introduced into the superior mediastinum and flushed with 5 ml of saline. Both catheters were connected to Statham venous pressure transducers linked to an Offner 411 recorder. Mediastinal and central venous pressures were recorded following the mediastinal injection of dextran-70 in 0.9% saline.

Both mediastinal and central venous pressures rose markedly during dextran injection (fig 5). Following a short period for stabilization and recalibration, marked respiratory fluctuations (4 torr) were observed in the mediastinal pressure. The

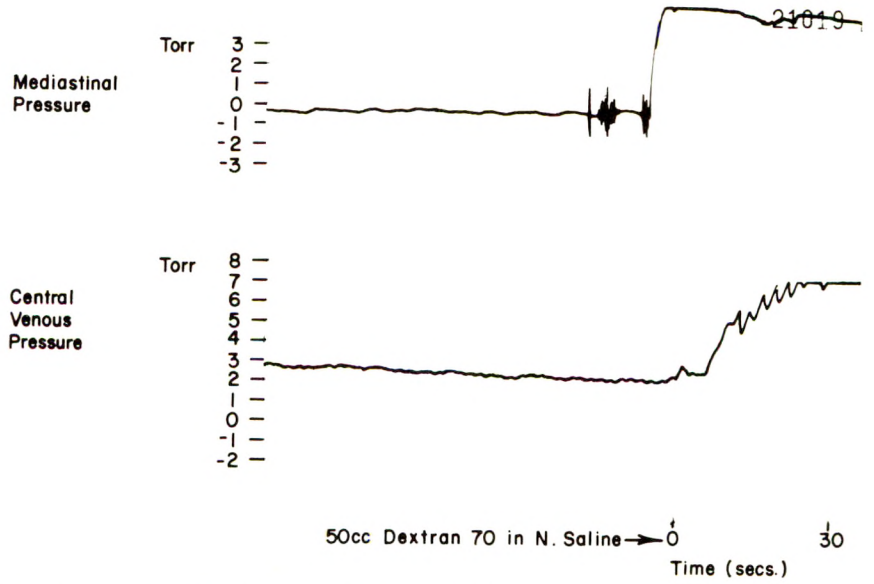


FIG 5. Comparison of mediastinal and central venous pressures during injection of dextran into the mediastinum of a dog.

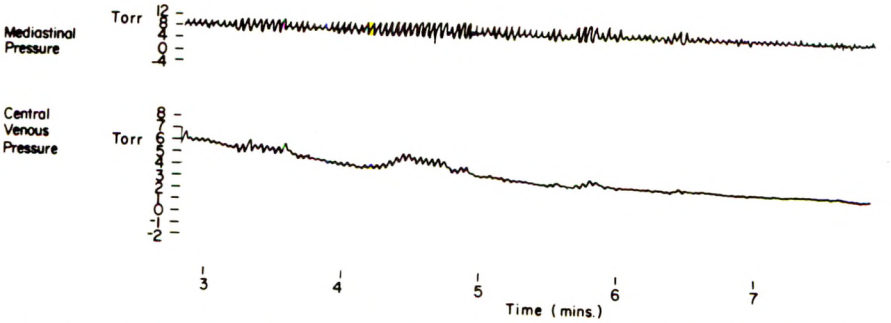


FIG 6. Mediastinal and central venous pressure fluctuations in dog with fluid-filled mediastinum.

maximum fluctuation of venous pressure with ventilation was 1.5 torr (fig 6). The position of both catheters was confirmed at subsequent thoracotomy, when a right hydrothorax and hydromediastinum were noted.

These findings confirm the clinical experience that a CVP catheter that has migrated into a fluid-filled mediastinum can show fluctuations of pressure, these fluctuations being similar to, and possibly greater than, those in a central venous catheter. In the case described here, it is probable that, either during or after insertion, the CVP cannula perforated the left internal jugular vein and entered the mediastinum, which, being filled with blood, simulated the central venous system. Subsequent infusion of 5% dextrose in lactated Ringer's solution and Renografin-60® resulted in a tension hydrohemo-Renografin thorax which resolved with appropriate therapy.

It is concluded that central venous cannulation by any route should be regarded with great circumspection in any patient who may have mediastinal bleeding. Unless immediate thoracotomy is to be done, confirmation of catheter placement should be sought by injection of a radiographic contrast medium.

ACKNOWLEDGMENT

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Intraoperative Hyperthermic Crisis in Two Children with Undifferentiated Lymphoma

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THE malignant hyperthermia syndrome can be initiated by almost all anesthetic agents and can occur with or without rigidity. The basic defect probably lies in the sarcolemma reticulum, which is the calcium storing and release organ of muscle tissue.

The etiology of this rare, but potentially fatal syndrome is unknown. The disorder is transmitted as an autosomal dominant in some, but not all patients. The syndrome has occurred in association with musculoskeletal diseases. It has also been suggested

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that malignant hyperthermia may be a manifestation of a generalized stress syndrome, a vicious cycle involving skeletal muscle and catecholamine secretion.[1] Recently Schiller and Mair demonstrated a viruslike crystalline structure in the muscle biopsies taken in the acute stage of two fatal malignant hyperthermia cases which suggests another possibility, that of a viral etiology.[2]

We report two cases of hyperthermic crises which occurred in children who suffered from widely metastasizing undifferentiated lymphoma. Both children exhibited similar fulminant clinical courses and crises. These were nonrigid in form and there was no history of malignant hyperthermia in either family. The histological diagnosis was consistent with Burkitt's lymphoma.

REPORT OF CASES

Case 1 — A four-year-old, previously healthy, white male weighing 17 kg developed acute onset of abdominal distension, with symptoms compatible with intestinal obstruction. He was scheduled for an exploratory laparotomy for a large mass anterior to the rectum. The preoperative temperature was 37.6 C, the blood pressure 100/72 torr, the pulse rate 102/min, and the respiratory rate 20/min. Hemoglobin was 11.7 g%, white blood count 13,100, and blood urea nitrogen 8 mg%, and serum electrolytes were within normal limits. The chest roentgenogram was normal.

The patient was premedicated with meperidine 15 mg and atropine 0.2 mg IM. Anesthesia was induced with thiopental 50 mg IV. Tracheal intubation was facilitated with succinylcholine 20 mg IV. There was no muscle rigidity. Anesthesia was maintained with 1.0 to 1.25% halothane in a 50% mixture of N_2O and O_2. Muscle relaxation was provided by pancuronium 1 mg IV.

Approximately 30 minutes after induction of anesthesia, the esophageal temperature was 38.9 C and the pulse rate had increased from 150 to 180/min. Ice packs were applied to the neck and axilla but the temperature continued to rise rapidly, reaching 40.4 C 20 minutes later. The pulse rate increased further to 200-210/min and the patient developed multifocal ventricular contractions interspersed with runs of ventricular tachycardia. These aberrant rhythms did not respond to IV lidocaine, propranolol, or sodium bicarbonate. The abdominal cavity was irrigated with cold saline solution, which brought the temperature down to 36.5 C in approximately 15 minutes. The pulse rate returned to 140/min and the arrhythmias disappeared. Biopsies were taken from the tumor and the abdomen was closed. The tumor filled the entire pelvis, involving both small and large bowels with widespread metastases to mesentery, omentum, and stomach. The liver and spleen appeared intact. The anesthesia time was 1 hour and 30 minutes.

In the recovery room the patient was lethargic but responsive, with stable vital signs. Marked metabolic acidosis (base excess of −15.0 mEq) was corrected with IV sodium bicarbonate. The temperature gradually stabilized at 38.1 C. Blood cultures taken in the recovery room were reported as negative at a later date. On the ward, the patient was treated with vincristine, cyclophosphamide, and radiation therapy. Signs of intestinal obstruction continued. The patient became comatose during the 4th week postoperatively and expired during the 7th week. Autopsy permission was not granted.

There are 7 siblings in both the mother's and father's family, including 6 females and 8 males. The father of our patient had surgery under general anesthesia without complications. Two siblings of the mother also had complication-free surgery. The only sibling of the deceased patient is healthy and has never had anesthesia.

Biopsy specimens obtained from the greater curvature of the stomach, omentum, mesentery, and liver showed undifferentiated malignant lymphoma consistent with Burkitt's lymphoma. The malignancy was comprised of uniform primitive cells with round nuclei containing several prominent nucleoli. These were interspersed by small clean spaces containing histiocytic cells, with evidence of nuclear karyorrhesis and fragmentation. The low-power microscopic appearance was that of "starry sky" pattern.

Case 2—A 13-year-old white male weighing 34 kg was admitted to a local hospital in 1968 for painless rectal bleeding. The patient was scheduled for an exploratory laparotomy. The patient was premedicated with meperidine 50 mg and atropine 0.3 mg IM. Anesthesia was induced with thiopental 150 mg IV. Tracheal intubation was facilitated with succinylcholine 40 mg IV. Anesthesia was maintained with halothane in a mixture of N_2O and O_2. Muscle relaxation was provided by d-tubocurarine (18 mg). A large

gelatious pelvic mass involving ileum was excised and a right hemicolectomy was performed. The anesthetic course was uneventful at this time. Microscopically, the tumor was a lymphoblastic lymphosarcoma with scattered histiocytes, giving striking "starry sky" appearance consistent with Burkitt's lymphoma. The patient was treated with cyclophosphamide and then methotrexate with a favorable response. He was discharged from the hospital.

Three months later, the patient was readmitted because of recurrence of the tumor. He was scheduled for a retroperitoneal lymph node biopsy. He had a low-grade fever and a tachycardia of 120/min. His temperature was 37.8 C, hemoglobin 13.1 g%, white blood count 9600, and blood urea nitrogen 24 mg%. The patient was premedicated with meperidine 50 mg and atropine 0.3 mg% IM. Anesthesia was induced with thiopental 150 mg IV. Tracheal intubation was facilitated with succinylcholine 40 mg IV. There was no documentation of muscle rigidity in the anesthesia record. Anesthesia was maintained with halothane in a mixture of N_2O and O_2. Toward the end of the 45-minute procedure, the patient developed a tachyarrhythmia and warm skin. The rectal temperature at the conclusion of the procedure was 40.4 C. The patient developed cardiac arrest, from which he was successfully resuscitated. He was rapidly cooled by sponging with cold water. Kanamycin was given after blood specimens were obtained for culture. The patient improved slowly, but approximately 2½ hours later developed another cardiac arrest, which did not respond to cardiac resuscitative measures. Blood cultures were reported as negative at later date.

A sibling of the patient's mother and the patient's father had surgery in the past without anesthetic complications. The only sibling of the deceased had an operation without an anesthetic complication. No other pertinent family history was available.

Autopsy showed widespread metastasis involving pericardium, pleura, gastrointestinal tract, liver, gall bladder, pancreas, spleen, kidneys, urinary bladder, ureter, mesentery, diaphragm, abdominal wall, and lymph nodes. Histologically, the tumor was a lymphoblastic lymphosarcoma consistent with Burkitt's type but the striking phagocytic activity giving "starry sky" appearance observed in the previous specimen was less prominent.

COMMENT

Because of the limited sampling, a genetic relationship could not be ruled out in these two cases. However, there does not appear to be such a relationship since neither siblings, parents, nor parents' siblings had adverse reactions to general anesthesia. In one patient, the previous anesthetic course was uneventful only 3 months prior to the hyperthermic crisis, suggesting that the etiology of the hyperthermia was acquired rather than genetic in origin.

The histological diagnosis in both children was consistent with undifferentiated lymphoma of Burkitt's type, which is the only lymphoma known to carry Epstein-Barr virus (EBV). Although 97% of African Burkitt's lymphomas have EBV-DNA in the tumor cells, only 8 to 17% of the American counterparts carry EBV genome equivalents. The seroepidemiological data also parallel the above EBV association in African and American Burkitt's lymphoma.[3] The etiological relationship, therefore, between the virus and tumor cannot be established but fluctuations of antibodies which occur during the clinical course of this disease suggest the presence of virus-related factors.[4] Recently, ultrastructural study[5] has demonstrated in tumor cells of an American Burkitt's-type lymphoma the presence of cytoplasmic tubular arrays, which were thought to represent nucleocapsids of an unidentified virus or antibody in response to viral antigens.

The malignant hyperthermia which occurs with muscle rigidity is usually hereditary and is often associated with musculoskeletal diseases. In contrast, the family history is much less frequent in nonrigid malignant hyperthermia and the etiology in this group is unknown.[6] In this context, it is of interest that Tang et al for the first time isolated crystalline particles in the muscles of a myopathic patient, and identified them as a virus.[7] This suggests that the previously described viruslike crystalline particles in the muscles of two malignant hyperthermia patients and in a victim of heat stroke[8] might indeed be virus and supports Schiller's hypothesis that malignant hyperthermia could result from viral myopathy in some patients.[9]

This raises a question concerning the etiology of hyperthermic crises in our patients. We can neither prove the cause-and-effect relationship between the hyperthermic crises and undifferentiated lymphoma of our pa-

tients nor can we dismiss a possibility that viral invasion and/or viral antibody interaction on the muscle-cell membrane occurred during the fulminant stage of the disease. It is also possible that abnormal calcium and/or magnesium metabolism was present in the muscle and/or bone tissue. Additional reports and further investigation may clarify these possibilities.

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MORPHINE AND CORONARY BLOOD FLOW

Because morphine has been shown to cause coronary vasoconstriction in conscious dogs, human coronary blood flow was measured with the thermodilution technic before and after administration of morphine sulfate, 0.2 mg/kg body weight (maximum 15 mg) IV, in 10 patients to determine if the canine experience is clinically applicable. Coronary blood flow increased from a baseline value of 104.4 ± 13.4 (mean ± SE) to 113.0 ± 17.4 ml/min ($p>0.05$) 15 minutes after administration of morphine. Baseline coronary vascular resistance was 1.14 ± 0.19 mm Hg/ml/min; 15 minutes after morphine administration, the resistance averaged 1.02 ± 0.17 ($p<0.025$). There was no significant change between baseline values and values 15 minutes after morphine in systemic mean arterial pressure (98.2 ± 5.3 to 92.8 ± 4.7 mm Hg), heart rate (69.5 ± 3.5 to 72.6 ± 3.4 beats/min), left ventricular ejection time (0.345 ± 0.009 to 0.342 ± 0.007 second), or tension-time index (2324 ± 128 to 2291 ± 149 mm Hg/sec/min). The slight coronary vasodilation noted after morphine administration in this study is in contrast to the significant coronary vasoconstriction produced by morphine in the unanesthetized dog. *(Leaman DM, Nellis SH, Zelis R, et al: Effects of morphine sulfate on human coronary blood flow. Am J Cardiol 41:324-326, 1978)*

Correspondence

BACTERIAL FILTER RESISTANCE

To the Editor:

I am concerned about the data and conclusions presented by Dr. Edward Loeser in his article "Water-induced resistance in disposable respiratory-circuit bacterial filters" (Anesth Analg 57:269-271, 1978).

Dr. Loeser first contacted our company in September 1977 regarding his program for testing disposable anesthesia filters. He was told at that time that we had developed, were manufacturing, and were selling a Nicholes 99 filter with a hydrophobic coating to prevent occlusion by water without impairment of biologic filtration efficiency. At this time Dr. Loeser stated that "the K + G filter [even] without the hydrophobic coating was safe for anesthesia usage."

Dr. Loeser offered to include the new Nicholes 99 hydrophobic filter in his test program and was provided with filters and supportive data for this purpose. He nevertheless selectively excluded the hydrophobic filters from his study and failed to report data on their function in the article cited. Furthermore, had Dr. Loeser employed a relative humidity more relevant to normal clinical conditions he would have found, as have others, even the untreated Nicholes 99 filter to be fully acceptable since little or no water exists as a liquid in an anesthesia circuit during clinical use. It is only present as a vapor.

Every Nicholes 99 filter is thoroughly inspected and tested before shipment and there have been over one million Nicholes 99 filters used without a single problem of occlusion having been reported. The current Nicholes 99 filter is treated with a hydrophobic coating which acts to prevent occlusion by water but in no way impairs its unique functionality. Tests under exaggerated conditions show that long-term use (up to 29 hours) does not cause a drop in biological filtration efficiency (B.F.E.); nor does the $\triangle P$ (change in pressure) increase more than approximately 2 mm/H_2O at 100% relative humidity delivered at 37 C at 10 L air/min.

Harry R. Leeds
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CURARE SENSITIVITY IN MYASTHENIA GRAVIS

To the Editor:

We read with interest the case report of curare sensitivity in steroid-treated myasthenia gravis by Carol Lake.[1] We question Dr. Lake's conclusion that "steroids in myasthenia . . . clearly do not result in sufficient acetylcholine . . . to require a usual dose of nondepolarizing muscle relaxant." We have anesthetized a steroid-treated myasthenic who did not show curare sensitivity. Our patient presented in myasthenic crisis at age 52 in 1972. The patient's symptoms were initially controlled with pyridostigmine 180 mg per day. In April 1974, the patient was started on prednisone 60 mg daily, and the pyridostigmine was stopped. The prednisone was tapered to 20 mg on alternate days with minimal symptoms. In May 1977, the patient, weighing 81 kg, required a Nissen fundoplication for esophagitis. Anesthesia was induced with thiopental IV and N_2O-O_2-enflurane by mask; endotracheal intubation without relaxants was performed without difficulty. Additional relaxation required for surgery was obtained with 3-mg incremental doses of d-tubocurare given slowly over 30 minutes while hypothenar muscle twitch was monitored during ulnar nerve stimulation with a Block-Aid monitor. Satisfactory relaxation and loss of twitch required a total of 24 mg. Thirty minutes later another 3 mg of curare were needed. Reversal with neostigmine and atropine, 45 minutes later, restored twitch and sustained tetanus. In March 1978, the patient (73 kg), now on prednisone 30 mg every other day, required reconstruction of the Nissen fundoplication because of increasing regurgitation. Following preoxygenation and precurarization with 3 mg of curare, which produced no clinical weakness, rapid induction of anesthesia was achieved using 250 mg thiopental. While holding cricoid pressure, intubation was facilitated with succinylcholine 100 mg. About 6 to 8 minutes following the succinylcholine administration, twitch returned to control values. Anesthesia was maintained with N_2O-O_2-enflurane. Abdominal relaxation required 18 mg of curare initially, supplemented to a total of 30 mg over the next 3 hours. All doses were given in 3- to 6-mg increments

while twitch was monitored. Pyridostigmine restored twitch.

While both this patient and Dr. Lake's patients were similar in age, weight, and control of the myasthenic state with steroids, their responses to curare for relaxation were markedly different. The curare doses used in our patient are not unusual for surgical relaxation during enflurane anesthesia in normal patients, as Fogdell and Miller[2] have shown a reduction in the dose of curare needed during enflurane. Does curare sensitivity remain in steroid-treated myasthenics? While Dr. Lake's patient would indicate it does, our patient failed to demonstrate sensitivity. Hopefully others will submit their experiences to clarify this issue.

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The opinions or assertions in this letter are those of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

* * *

POLLUTION, A CAUSE FOR CONCERN 55 YEARS AGO, TOO

To the Editor:

Since current epidemiologic studies suggest that the operating room is a hazardous environment to the health of personnel, and since chronic exposure to trace amounts of the inhalational anesthetic agents has been implicated as a causative factor, it might be an interesting historical perspective to your readers to reprint one of the editorials published in the first issue of *Current Researches in Anesthesia and Analgesia* (1:18, 1922).

This Editorial/Obituary, "Noted Anesthetist Dies a Martyr to His Skill," contains some contemporary inferences and perhaps attests to the insight of the pioneers of our specialty.

The editorial reads as follows:

NOTED ANESTHETIST DIES A MARTYR TO HIS SKILL

When funeral services were recently read over the body of Dr. T. Edward Costain, of Chicago, several hundred physicians and surgeons of America lowered their heads in mourning for the passing of a martyr to science. Dr. Costain's colleagues say that he paid with his life for his humane work of giving anesthetics so that surgery would be relieved of its horror and patients of their pain.

An unusual feature in connection with the passing of Dr. Costain was that on his death bed he expressed the wish that the public be not informed of his death when it occurred, lest the medical profession will suffer a blow, when it became known that the administration of anesthetics had cost the life of the man who had spared more than 30,000 people suffering while undergoing operations.

At the recent meeting of the American Association of Anesthetists in St. Louis, Dr. Gilbert Fitz-Patrick, who had been associated with Dr. Costain for many years, said, "That while we have not been able to prove it definitely, still we have much evidence to show that the administration of anesthetics, over a long period of years, produces a condition of nephritis that results fatally. Dr. Costain has given 30,000 ether anesthesias and we, who have been studying his case, know the effect and result. We know what protective measures must be used by radiologists, but so far medical science has not discovered the protection required for those who give anesthetics."

About the time Dr. Costain was mortally stricken he was unanimously chosen President of the Chicago Society of Anesthetists. Last year he was also President of the Illinois Homeopathic Medical Association and for the past ten years has been a Trustee of the American Institute of Homeopathy, of which he was Secretary-Treasurer at the time of his death, as well as managing editor of its official journal.

He was 59 years of age having been born on the Isle of Man in 1863. He was educated in America and graduated from the Chicago Homeopathic College of Medicine more than thirty years ago. He has been a Professor of Anesthesia at Hahnemann Medical College for many years. Dr. Costain was interred at Freyeberg, Maine, the home of Mrs. Costain, who survives him. The Association of Anesthetists extend her their heartfelt sympathy in her bereavement and wish her the consolation which so exceptional a life and martyrdom must afford—*McM.*

(J. H. McMechan, MD, Editor)

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Book Reviews

Immediate Care, by John S. M. Zorab and Peter J. F. Baskett, 269 pp, Philadelphia, W. B. Saunders Company, 1978.

Immediate Care is a wide-ranging 'what-should-be-done' rather than a 'how-to-do-it' book. The problems that authors and readers have when cutting across many specialty boundaries are discussed in the Preface. Its goal is to present information relevant to doctors who handle emergencies—including family practitioners (and presumably medical students). Immediate care is defined on page 203 as treatment: (1) on site, (2) during transportation, and (3) in the emergency department.

The authors are anesthetists and intensivists in a regional accident center of a major teaching hospital. Both have published previously on immediate care (eg *The Management of Cardiac Arrest,* Zorab, Churchill Livingstone, 1972).

Paraphrasing, the book is divided into four sections and twenty chapters:

I. Basic care - (Chapter 1) Introduction, (2) Respiratory, (3) Cardiovascular, (4) Analgesia and Anaesthesia

II Trauma - Injuries of: (5) Head, (6) Face, (7) Chest, (8) Limbs, (9) Spinal, (10) Abdomen, (11) Burns

III. Non-traumatic - (12) Myocardial infarction, (13) Acute respiratory insufficiency, (14) Poisoning, (15) Diabetes, (16) Drowning and hypothermia

IV. General - (17) Organization, (18) Immediate care, (19) Training, (20) Equipment.

The liberal use of advanced organizers and side headings make the short paragraphs read easily. The references are impressively current primary sources—mainly from the British literature.

Specialists in immediate care will find this book useful to compare American and British practices, and as a source of references to the British literature. The emphasis on pain control in emergency work is impressive and the use of Entonox (pre-mixed 50% nitrous oxide, 50% oxygen) is stressed. This Pandora's box of pain control in immediate care has barely been opened in American theory and practice. The Glasgow coma chart (page 59) could be adopted in the United States to help document changing states of consciousness more closely.

In my opinion, it would be a mistake for the American student to use this book for two reasons:

1. The basic information on airway control, resuscitation, and advanced life support has been systematized and is presented with far greater clarity in the American literature—thanks to the efforts of the Department of Transportation, the American Heart Association, the American National Red Cross, the State Emergency Medical Services movement, and other concerned authorities.

2. American practices differ radically from some of those recommended. Examples abound: The American Heart Association recommends a ratio of 2 ventilations to 15 compressions in one-person cardiopulmonary resuscitation, not 2:8; the jaw thrust is barely mentioned; the esophageal airway is not included; splinting for fractures is almost completely dismissed; traction on the head while applying a cervical collar or short spineboard is not mentioned; some of the drugs discussed are not available here; those that are may have different names.

This book demonstrates the vast duplication of basic and clinical research effort that occurs at the national level. Despite electronic age communication and a common language, it is apparent that we behave as products of particular cultures, not as citizens of planet Earth.

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Books Received

Title	Author/Editor	Publisher	Price Pages
Malignant Hyperthermia	Antonio J. Aldrete Beverly Britt	New York Gruen and Stratton, Inc. 1978	$25.50 560 pp
Handbook of Clinical Pharmacology	Felix Bochner George Carruthers Jens Kampmann Janice Steiner	Boston Little, Brown and Company 1978	$9.95 313 pp
Factors Influencing Vascular Reactivity	Oliver Carrier Shoji Shibata	New York Igaku-Shoin Medical Publishers, Inc. 1977	$38.00 296 pp
Enzymes in Anesthesiology	Francis F. Foldes	New York Springer-Verlag 1978	$34.80 368 pp
Clinical Anesthesia Procedures of the Massachusetts General Hospital	Phillip W. Lebowitz	Boston Little, Brown, and Company 1978	$10.95 437 pp
Recent Advances in Intensive Therapy	I. McA Ledingham	New York Churchill Livingstone 1977	$23.00 257 pp
Clinical Pharmacology Second Edition	Kenneth L. Melmon Howard F. Morrelli	New York Macmillan Publishing Company, Inc. 1978	$25.00 1146 pp
The Apallic Syndrome	G. Dalle Ore F. Gerstenbrand C. H. Lucking W. Peters U. H. Peters	New York Springer-Verlag 1978	$41.40 259 pp
Monitoring in Anesthesia	Lawrence J. Saidman N. Ty Smith	Sumerset John Wiley and Sons, Inc. 1978	$25.00 356 pp

A Guide for Authors

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For books:

> Avery MA, Fletcher BD: The Lung and Its Disorders in the Newborn Infant. Third edition. Philadelphia, W.B. Saunders Co., 1974, pp 54-58

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> Phillips OC, Capizzi LS: Anesthesia mortality, in Public Health Aspects of Critical Care Medicine and Anesthesiology. Edited by P Safer. Philadelphia, FA Davis Co., 1974, pp 219-224

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ACTION: ANTILIRIUM (physostigmine salicylate) is a salicylic acid derivative of an alkaloid extracted from seeds of Physostigma Venenosum (calabar bean). The action of the parasympathetic nerves is intermediated by the formation of acetylcholine at the peripheral end of these nerves. Physostigmine inhibits the destructive action of cholinesterase and thereby prolongs and exaggerates the effect of the acetylcholine.

Physostigmine contains a tertiary amine and easily crosses the blood brain barrier, while neostigmine contains a quaternary amine and is not capable of crossing the structure. This may explain why neostigmine does not cause reversal of anticholinergic-induced delirium while physostigmine does.

Dramatic reversal within minutes of coma, hallucinations, and other signs can be expected if the diagnosis is correct and the patient has not suffered anoxia or other insult. Therapeutic doses may be necessary at intervals as life-threatening signs recur. Physostigmine is destroyed in the body in 60 to 120 minutes.

CONTRAINDICATIONS: Physostigmine should not be used in the presence of asthma, gangrene, diabetes, cardiovascular disease, mechanical obstruction of the intestines or urogenital tract or any vagotonic state, and in patients receiving choline esters or depolarizing neuromuscular blocking agents.

WARNING: If excessive symptoms of salivation, emesis, urination and defecation occur, the use of ANTILIRIUM should be terminated. If excessive sweating or nausea occur, the dosage should be reduced.

Intravenous administration should be at a slow, controlled rate, no more than 1 mg. per minute (see dosage). Rapid administration can cause bradycardia, hypersalivation leading to respiratory difficulties and possibly convulsions.

An overdosage of ANTILIRIUM can cause a cholinergic crisis.

PRECAUTIONS: Because of the possibility of hypersensitivity in an occasional patient, atropine sulfate injection should always be at hand since it is an antagonist and antidote for physostigmine.

ADMINISTRATION AND DOSAGE: The usual adult dose of ANTILIRIUM is 0.5 to 2.0 mg. intramuscularly or intravenously. Intravenous administration should be at a slow, controlled rate of no more than 1 mg. per minute. It may be necessary to repeat dosages of 1 mg. to 4 mg. at intervals as life threatening signs such as arrhythmias, convulsions and deep coma recur.

IN ALL CASES OF POISONING, THE USUAL SUPPORTIVE MEASURES SHOULD BE UNDERTAKEN.

SUPPLIED: 2 ml. ampules containing: PHYSOSTIGMINE SALICYLATE 1 mg. per ml. Packed 12 ampules per box.

NDC 0456-1037-12

CAUTION: Federal law prohibits dispensing without prescription.

REFERENCES:

Greene, L. T.: Physostigmine treatment of anticholinergic drug depression in postoperative patients. Anesth & Analg, March-April 1971; 50-2: 222-226.

Rumack, B.: Anticholinergic poisoning: Treatment with physostigmine. Pediatrics, Sept. 1973.

Slovis, T. L., Ott, J. E., Tietelbaum, D. T., and Lipscomb, W.: Physostigmine therapy in acute tricyclic antidepressant poisoning. Clinical Toxicology, 4:451, 1971.

O J O'NEAL, JONES & FELDMAN

Classified Advertising

MEDICAL OFFICER (ANESTHESIOLOGY) needed at Gorgas Hospital, a fully accredited, 300-bed general teaching hospital operated by the U. S. Government in the Panama Canal Zone. The position is that of Chief, Anesthesia and Operative Service, Gorgas Hospital. Applicants must be citizens of the United States Certification by the American Board of Anesthesiology is desirable. Entrance salary is $44,870.45 a year (includes 15% tropical differential). Benefits include free transportation to Canal Zone for appointee, eligible dependents and household goods; free shipment of automobile from New Orleans to the Canal Zone; approximately two months leave earned annually; round-trip transportation to U. S. place of residence every two years; U. S. Government operated schools from kindergarten through junior college; Government sponsored life and health insurance programs; U. S. Civil Service retirement benefits; year-round tropical climate; and opportunities for economical tourist travel to Central and South America, and some Caribbean countries. Airmail Personal Qualifications Statement (SF-171, available in some post offices or Government agencies) or inquiry to: Chief, Personnel Operations Division; Box 2012; Balboa Heights, Canal Zone; Attn: Chief, U. S. Recruitment Section; Dept. AA.

AN EQUAL OPPORTUNITY EMPLOYER

EXCELLENT OPPORTUNITY—ANESTHESIOLOGIST: Board eligible, or certified, to replace retiring member of a group of six anesthesiologists and six CRNAs in new, 307-bed hospital located in medium-sized New England city. Salary and corporate benefits first year with full participation to follow. Box 7-78-B, c/o I.A.R.S.

ANESTHESIOLOGIST: FMG. Board eligible; passed Part I. Two years in private practice, University trained. Planning to relocate for fee-for-service basis. Available anytime. Reply to: P.O. Box 16381, Lubbock, Texas 79490. Telephone: (806) 799-5714.

TEXAS—Board Certified or Board Eligible Anesthesiologist wanted to join department consisting of Board Certified Anesthesiologist and 4 CRNA's in 392 bed acute hospital. Caseload consists primarily of general surgery, gynecology and minimal OB coverage. Fee for service practice with generous first year salary guarantee. Texas malpractice rates are minimal and there is no state income tax. Amarillo has 170,500 pop., low housing and utility costs and a very modern medical center. For further details contact: Robert C. Pearson, Office of Professional Recruitment, Amarillo Hospital District, P.O. Box 1110, Amarillo, Tx. 79175, (806) 376-4431, ext. 330 or contact John Kaczmarek, M.D., (806) 359-5338.

ANESTHESIOLOGIST NEEDED TO JOIN 5-MAN department in 100 doctor multispecialty clinic with adjacent hospital; excellent salary and benefits leading to full partnership; community of 100,000 containing large midwestern university including medical school; faculty association available. Write Medical Director, Carle Clinic, Urbana, IL 61801.

CONNECTICUT — Candidate for Department Director of Anesthesiology sought in modern, 620-bed teaching community hospital, major affiliate of Yale University School of Medicine. 11 anesthesiologists, 9 nurse anesthetists function as group. Approved teaching program with full-time faculty, all clinical departments. Ideal opportunity for aggressive, innovative anesthesiologist desiring leadership role in developing academically superior Department with corollary intensive care consultative functions. All financial arrangements negotiable. Address: C. Bushnell, Exec. V.P., Bridgeport Hospital, Bridgeport, Connecticut 06602.

Applications are invited for the **CHAIR OF ANESTHESIOLOGY**, State University of New York, Downstate Medical Center, Brooklyn, New York. Candidates, and those wishing to nominate candidates, are asked to send curriculum vitae to: Dr. William Shucart, Chairman, Search Committee, Dept. of Neuro-Surgery, SUNY-DMC, 450 Clarkson Avenue, Brooklyn, New York 11203. Equal opportunity, affirmative action employer.

ANESTHESIOLOGISTS: Immediate opening for two anesthesiologists, preferably Board certified, in modern university-affiliated teaching hospital. Applicants must be experienced in cardiac, thoracic, major vascular and neurosurgical anesthesia. No OB. Compensation attractive and negotiable. Send curriculum vitae and references to Director of Anesthesiology, The Miriam Hospital, 164 Summit Ave., Providence, R. I. 02906.

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Childrens Hospital of Los Angeles

Three-phase program: Clinical, Academic, Investigative, emphasizing practical aspects of anesthesiology related to infants and children.

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Childrens Hospital of Los Angeles
4650 Sunset Boulevard
Los Angeles, California 90054
Phone (213) 660-2450, Ext. 2262

Classified Advertising (Continued)

CLINICAL DIRECTOR OF OPERATING ROOM SERVICES

Methodist Hospital of Indianapolis, Indiana, is seeking a board certified anesthesiologist to assume responsibility for clinical direction of its Obstetrical Anesthesia, Operating Room and Recovery Room Services. Methodist is a 1200-bed medical center offering a wide range of practice opportunities. Volume: 26,000 general surgical and 3,900 OB procedures per year.

The primary focus of this position is provision of obstetrical anesthesia, supervision of staff CRNAs and management of clinical activities in these areas. The opportunity to participate in general surgical procedures is also available. These activities are carried out in conjunction with other hospital staff anesthesiologists.

Previous experience in all areas of anesthesia with a special interest in obstetrical activity are necessary. An interest in administration or demonstrated ability to manage are vital. Salary and benefits are competitive and commensurate with experience.

Please contact: Dr. William Karsell, Chairman
Physician Recruitment
Committee
(317) 924-8038.

POSITION AVAILABLE

Wayne State University College of Medicine and Children's Hospital of Michigan are undertaking a joint search for an individual to head the Department of Anesthesiology at Children's Hospital of Michigan. The position will carry an appropriate academic rank as a member of the full-time faculty of the Department of Anesthesiology at Wayne State University. Interested persons should send a copy of their curriculum vitae and bibliography to:

Eli Brown, MD
Department of Anesthesiology
Wayne State University
College of Medicine
540 E. Canfield
Detroit, Michigan 48201

A Private, Voluntary Non-Profit Organization

Anesthesiologist wanted for a four-man incorporated group of Anesthesiologists practicing in Michigan. Community has a population over 200,000. No Obstetrics. Must be Board eligible or certified. Salary and benefits commensurate with training and experience. Send C/V to Box 7-78-A, c/o I.A.R.S.

DEPARTMENT ANESTHESIOLOGY CHAIRMAN: 83 member multispecialty group adjacent to modern accredited 480-bed hospital seeks experienced, Board Certified anesthesiologist to assume the position of Department Chairman and join two other physician anesthesiologists in practice; also to supervise large staff of CRNAs and qualified School of Anesthesia. Located in upper midwest university metropolitan area of 105,000; 35 minutes from superb lake region; associated with four year medical school; outstanding income; all specialties represented. Will pay travel expenses for physician and spouse for interview. Write to Box 5-78-D, c/o I.A.R.S., 3645 Warrensville Center Rd., Cleveland, Ohio 44122.

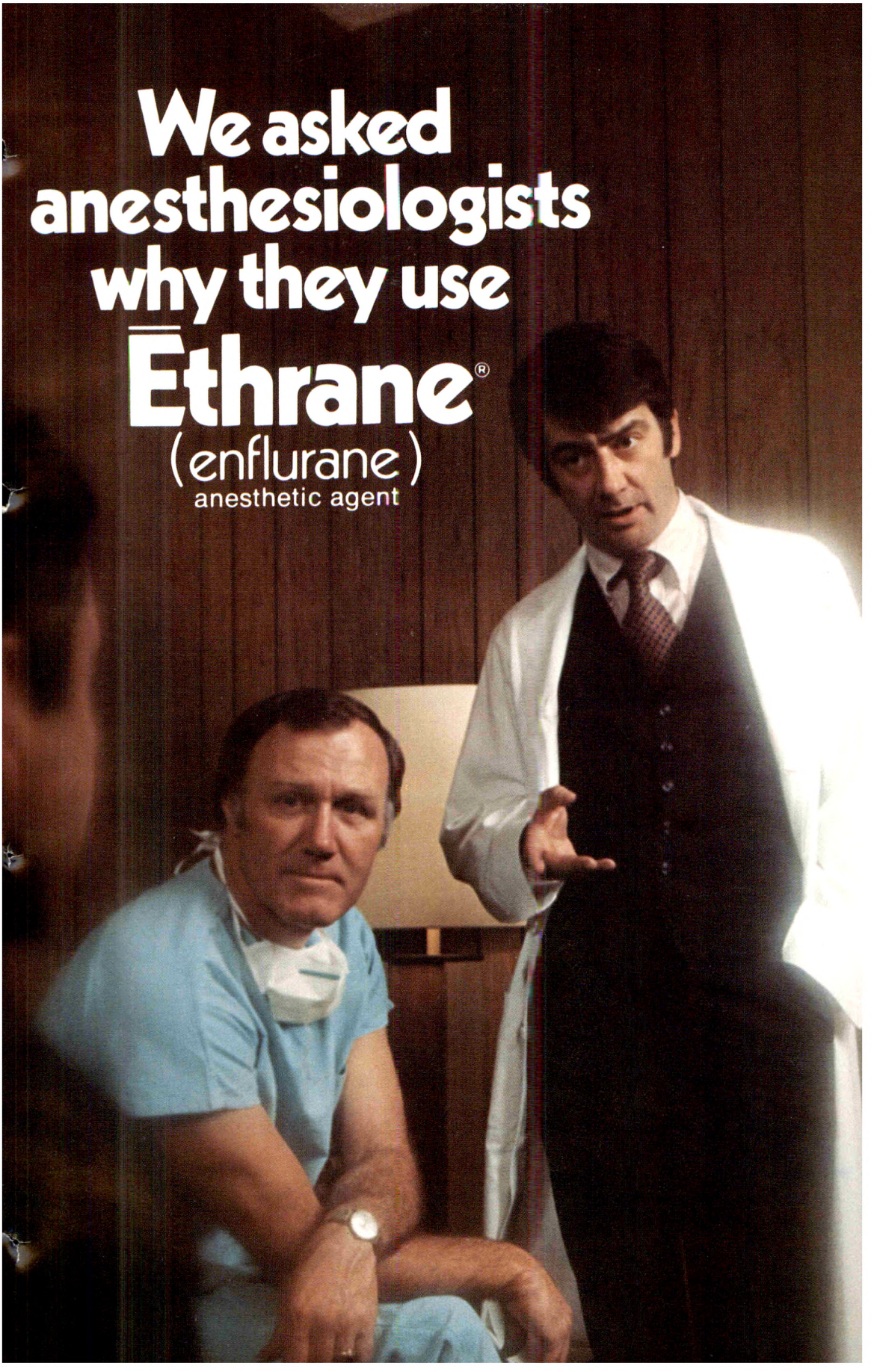
RESEARCH FELLOWSHIP: Approved for specialized year in Anesthesiology. Basic Science Studies in Clinical Pharmacology and Physiology. Outstanding facilities for diversified laboratory experiments. Direct inquiries to Dr. Hideo Nagashima, Montefiore Hospital, Anesthesia Department, 111 East 210th Street, Bronx, New York 10467. (212-920-4316).

"ALASKA" ANESTHESIOLOGIST:

Immediate opening for a Board certified or eligible anesthesiologist at Indian Health Service referral hospital. Contact Kenneth Petersen, M.D., Medical Director, Alaska Native Medical Center, Box 7-741, Anchorage, AK. 99510—(907) 279-6661.

ANESTHESIOLOGIST WANTED — 300-bed, general medical and surgical hospital with residents and university affiliation. Must qualify for either a commission in the U.S. Public Health Service Corps or a U.S. Civil Service appointment. An equal opportunity employer. Send curriculum vitae to: Chief, Department of Surgery, USPHS Hospital, 15th & Lake Street, San Francisco, California 94118, or call (415)-752-1400.

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(enflurane)
anesthetic agent

"Why do we use Ethrane® (enflurane)?"

"When you have an anesthetic agent like Ethrane which you can so predictably control—and it gives you muscle relaxation —that's a real advantage."†

Muscle relaxation with Ethrane usually is sufficient for lower and many upper abdominal procedures at normal levels of anesthesia. Should greater relaxation be required, the ability of Ethrane to potentiate the action of nondepolarizing agents permits significantly reduced dosage of these agents. This property of Ethrane may be particularly useful when supplemental relaxation is required toward the end of surgery.

"When patients wake up following Ethrane and demonstrate that they have control of their airway, and they have a satisfactory ventilatory exchange, I can send them back to a less controlled environment, with less monitoring, and feel comfortable."†

The low blood solubility of Ethrane* provides for its prompt elimination following surgery. Patients usually remain sedated for 10 to 20 minutes, then waken smoothly and rapidly with little or no postanesthetic effect. Vital signs return to preanesthetic levels promptly and patients are generally alert, without nausea and able to take fluids by mouth.

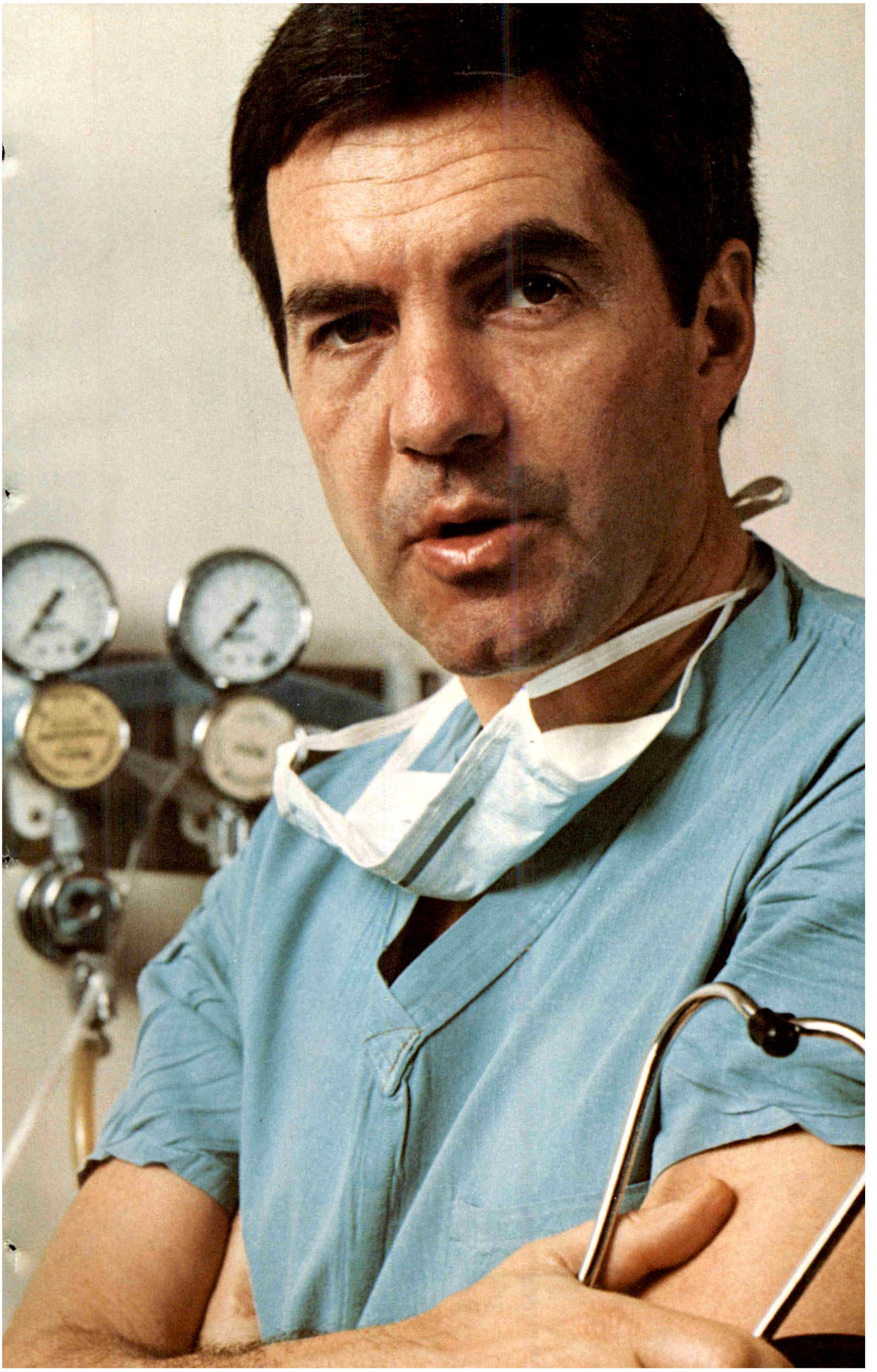
*Blood/gas partition coefficient: 1.9 @ 37°

†Excerpts from taped interview, anesthesiologist in Philadelphia, Pa., on file, Ohio Medical Products.

WARNING: Motor activity exemplified by movement of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia. For additional warnings, contraindications, and precautions, see following page.

Please see following page for complete product use information.

Ohio Medical Products

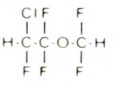


Ethrane® (enflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription

DESCRIPTION

ETHRANE (enflurane) is a nonflammable inhalation anesthetic agent. It is 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether, molecular weight 184.5, and its structural formula is:



The boiling point is 56.5°C at 760 mm Hg, and the vapor pressure (mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C. Vapor pressures can be calculated using the equation:

$$\log_{10} P = A + B/T \quad A = 7.967$$
$$B = -1678.4$$
$$T = °C + 273.16 \text{ (Kelvin)}$$

The specific gravity (25°/25°C) is 1.517. The refractive index at 20° is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C. The M.A.C. (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70% nitrous oxide and oxygen, and 1.17 in 30% nitrous oxide and oxygen.

ETHRANE is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No chemical stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary to maintain stability even in the presence of ultraviolet light. ETHRANE is stable to strong base and does not decompose in contact with soda lime and does not attack aluminum, tin, brass, iron or copper. The partition coefficients of ETHRANE at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride.

ACTIONS

ETHRANE (enflurane) is an inhalation anesthetic. Induction and recovery from anesthesia with ETHRANE are rapid. ETHRANE has a mild, sweet odor. There is mild stimulus to salivation or tracheobronchial secretions when ETHRANE is used alone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia changes rapidly with ETHRANE. ETHRANE reduces ventilation as depth of anesthesia increases. High pCO_2 levels can be obtained at deeper levels of anesthesia if ventilation is not supported. ETHRANE provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during ETHRANE anesthesia. ETHRANE anesthesia has been used in excision of pheochromocytoma in man without ventricular arrhythmias. On the basis of studies in patients anesthetized with ETHRANE and injected with epinephrine containing solutions to achieve hemostasis, up to 10 ml of 1:100,000 or 1:200,000 epinephrine containing solution may be injected subcutaneously at a rate of not more than 10 ml per minute and no more than 30 ml per hour. All customary precautions in the use of vasoconstrictor substances should be observed.

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with ETHRANE. THE NONDEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED. In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height. Neostigmine does not reverse the direct effect of ETHRANE.

Biotransformation of ETHRANE in man results in low levels of serum fluoride ions averaging 15 mM/L. These levels are well below the 50 mM/L threshold level which can produce minimal renal damage in normal subjects, however it is possible that these levels could result in damage in patients with severely impaired renal function or those undergoing renal transplantation. Depression of lymphocyte transformation does not follow prolonged ETHRANE anesthesia in man in the absence of surgery. Thus ETHRANE does not depress this aspect of the immune response.

INDICATIONS

ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Seizure disorders (see WARNINGS).

Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics.

WARNINGS

Increasing depth of anesthesia with ETHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentration usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental function testing does not reveal any impairment of performance following prolonged ETHRANE anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

The action of nondepolarizing relaxants is augmented by ETHRANE. Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from myoneural blockade will be longer in the presence of ETHRANE than for other commonly used anesthetics.

Usage in Pregnancy: Safety in pregnancy has not been established. Reproduction studies have been performed in rats and rabbits, and there is no evidence of harm to the animal fetus. The relevance of these studies to the human is not known. Since there is no adequate experience in pregnant women who have received the drug, safety in pregnancy has not been established.

PRECAUTIONS

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. ETHRANE (enflurane) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug. As with other general anesthetics and some muscle relaxants, hyperpyrexia has been observed with the use of ETHRANE.

ADVERSE REACTIONS

1. Motor activity exemplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia, or light levels with hypocapnia.
2. Hypotension and respiratory depression have been reported.
3. Arrhythmias, shivering, nausea, and vomiting have been reported.
4. Elevation of the white blood count has been observed.

DOSAGE AND ADMINISTRATION

The concentration of ETHRANE (enflurane) being delivered during anesthesia from a vaporizer should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for ETHRANE.
b) vaporizers from which delivered flows can easily and readily be calculated.

Nothing is present in the agent to alter calibration or affect the operation characteristics of the vaporizer.

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ETHRANE and the heart rate remains constant. The use of anticholinergic drugs is a matter of choice.

Induction: Induction may be achieved using ETHRANE alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the ETHRANE mixture. In general, inspired concentrations of 3.5-4.5% ETHRANE produce surgical anesthesia in 7-10 minutes.

Maintenance: Surgical levels of anesthesia may be obtained with 1.5-3% ETHRANE. Maintenance concentrations should not exceed 3%. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of ETHRANE concentration in the absence of other complicating problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Overdosage: In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish that the airway is clear and initiate assisted or controlled ventilation with pure oxygen as circumstances dictate.

PACKAGING

ETHRANE (enflurane) is packaged in 125 and 250 ml amber colored bottles.

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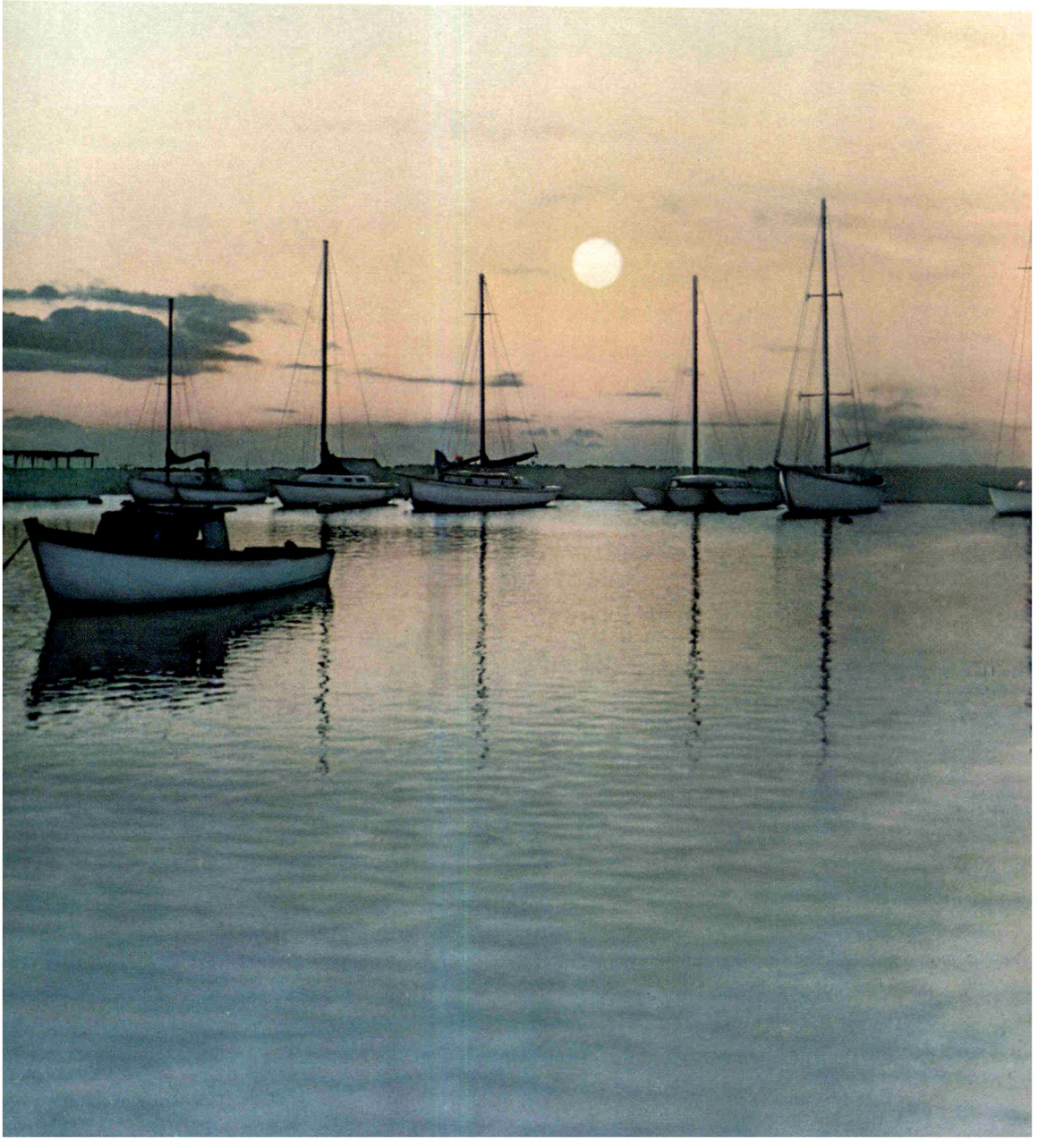
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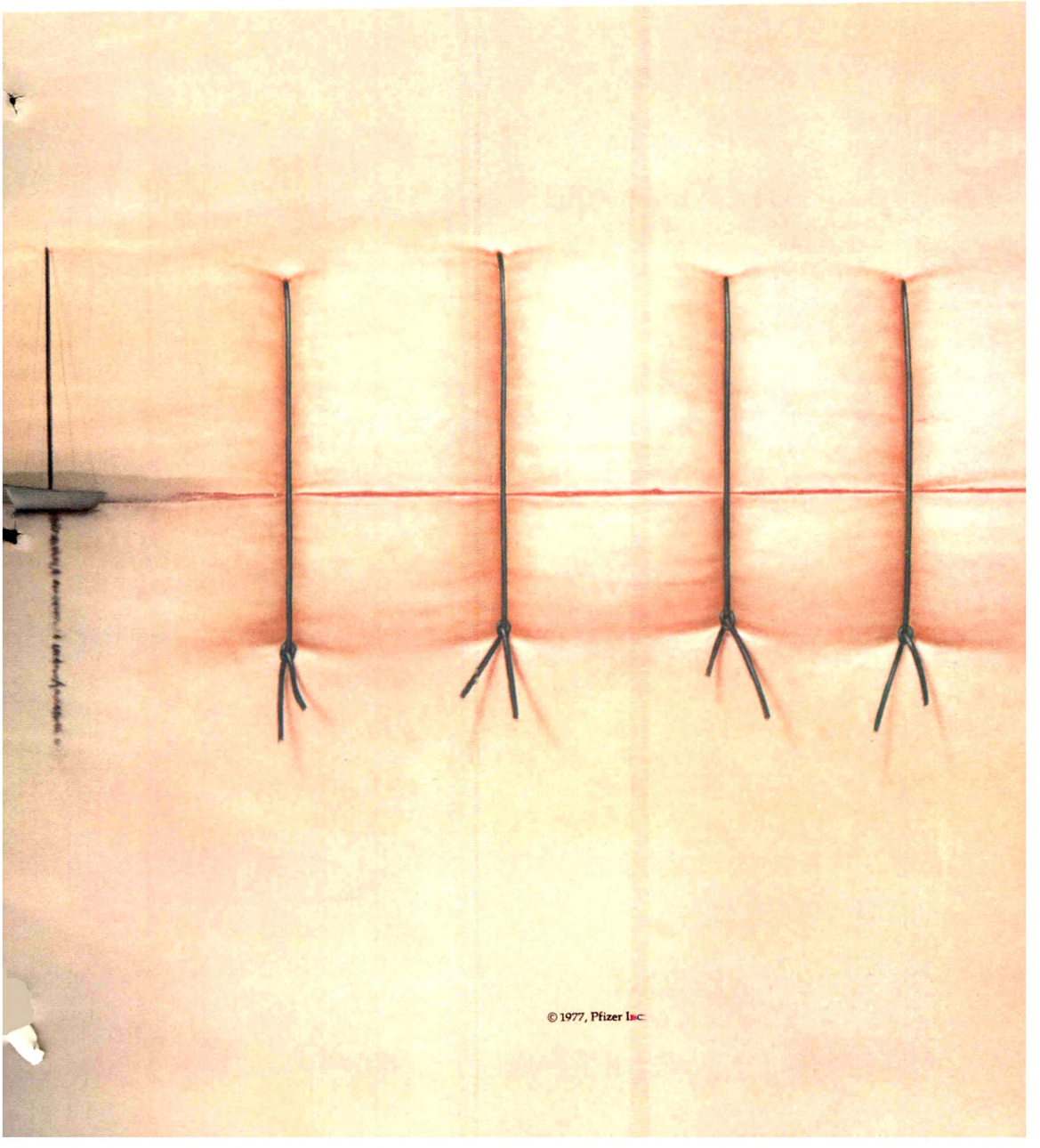


Vistaril® I.M.
(hydroxyzine HCl)

—allays anxiety
—reduces narcotic requirements
—and controls emesis

) surgery

Please see Brief Summary on following page for contraindications, precautions and adverse reactions.



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Vistaril® I.M.
(hydroxyzine HCl)
100 mg/2 ml—50 mg/ml and
25 mg/ml Vials and Isojects®

preoperatively and postoperatively

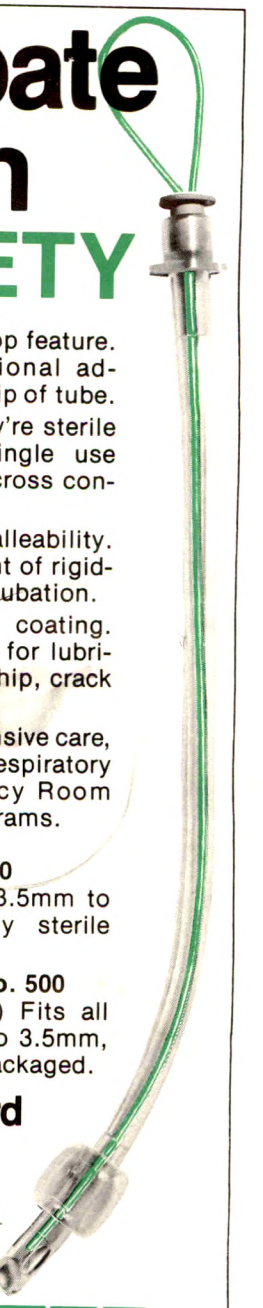
- **allays presurgical anxiety...allays the anxiety that may heighten the perception of postoperative pain**
- **may enhance the effects of analgesics and reduce narcotic requirements**
- **controls postoperative emesis**
- **vital signs are seldom impaired (Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.)**

BRIEF SUMMARY
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For Intramuscular Use Only
Contraindications: Hypersensitivity to hydroxyzine. The solution is for intramuscular use only and should not, under any circumstances, be injected subcutaneously, intra-arterially, or intravenously.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Since adequate data are not available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.
Precautions: HYDROXYZINE MAY POTENTIATE THE ACTION OF CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS AND BARBITURATES. In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. Inadvertent subcutaneous injection may result in significant tissue damage. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscles of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in order to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid inadvertent intravascular injection.
Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with doses considerably higher than those recommended.
Supply: Vistaril (hydroxyzine HCl) Intramuscular Solution: 25 mg/ml—10 ml vials; 50 mg/ml—2 ml and 10 ml vials; Isoject®, 25 mg/ml and 50 mg/ml—1 ml fill; 100 mg/2 ml—2 ml fill.
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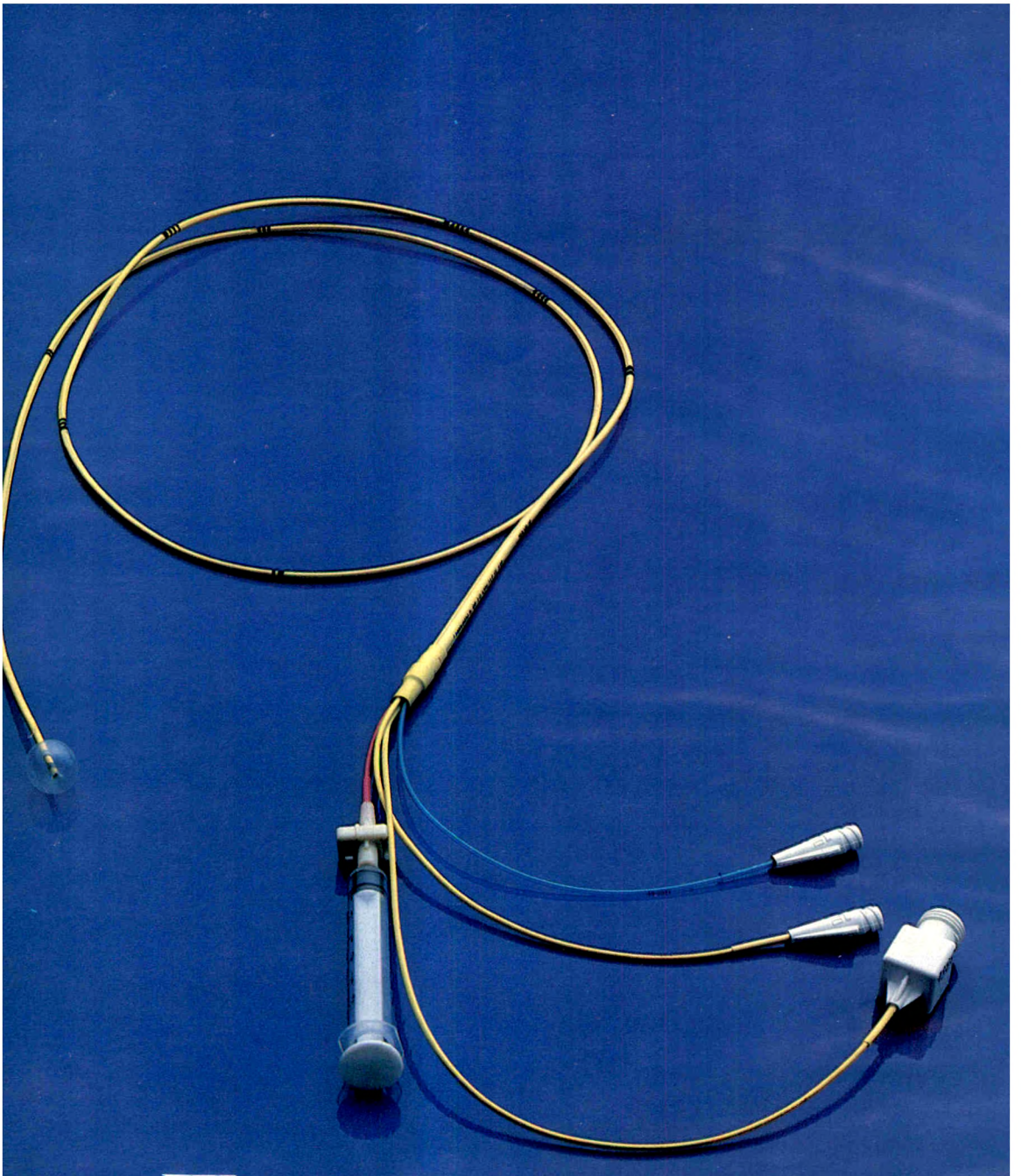
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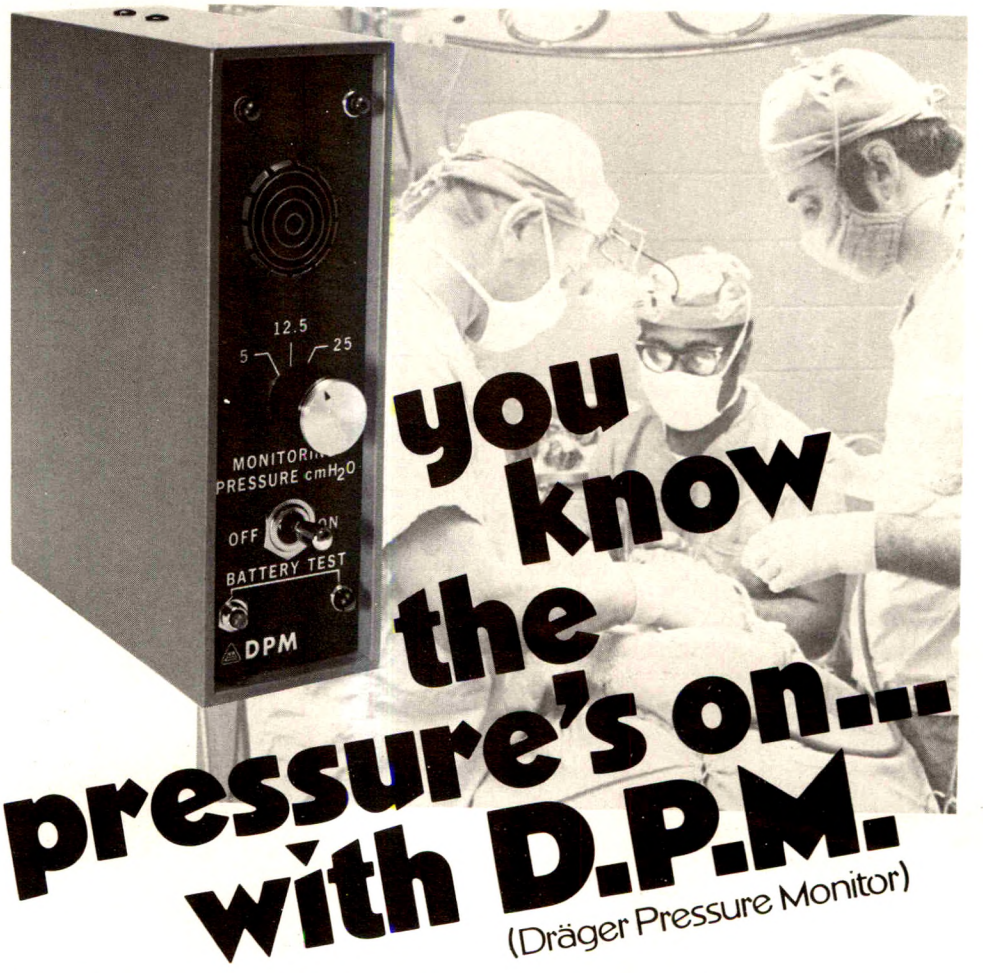


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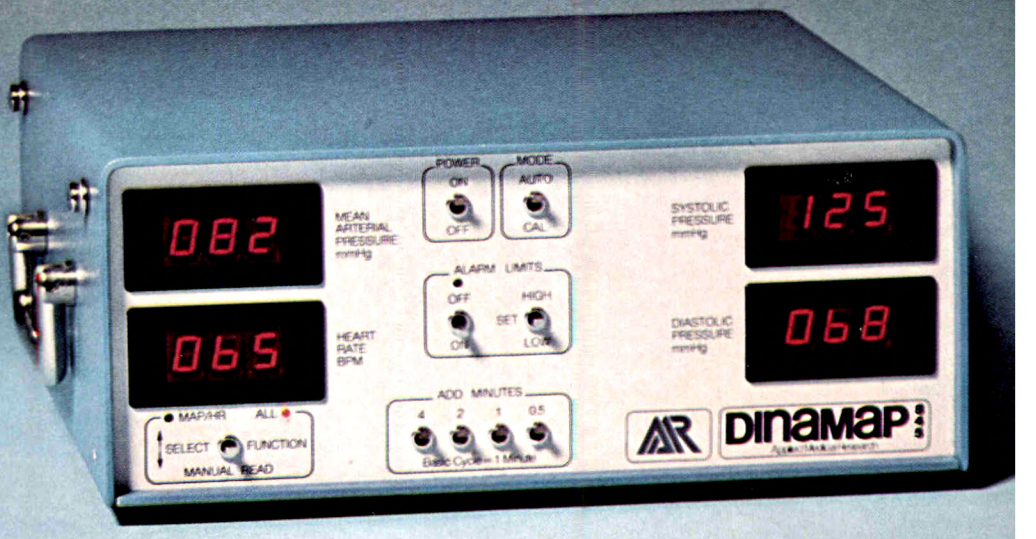
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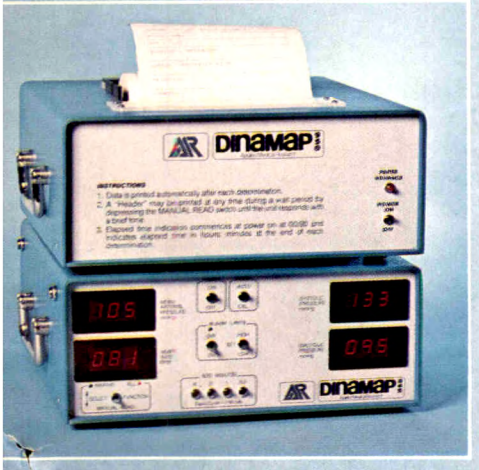
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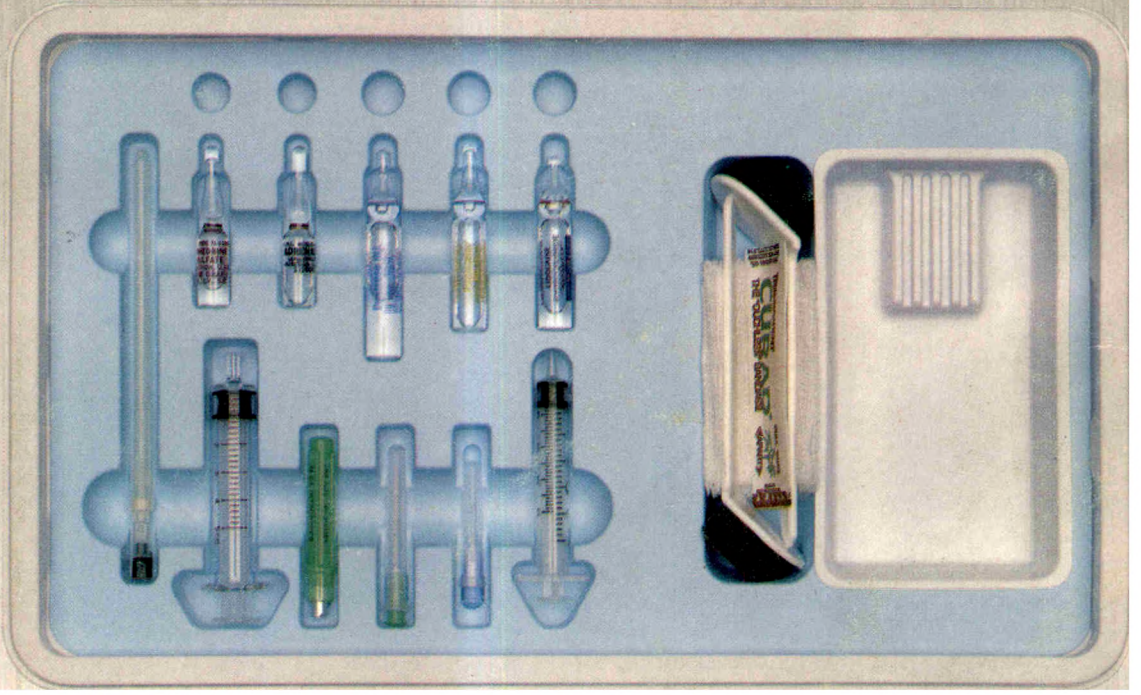


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Selected cases for Ketala

There are certain situations where the advantages of Ketalar suggest its serious consideration. Four such hypothetical situations are detailed here.
A fifth hypothetical case illustrates a situation in which Ketalar probably should be used only with caution.



Geriatric surgical procedure

Ketalar offers advantages in minor rectal surgery on elderly patients. When properly administered, Ketalar usually does not depress the patient's blood pressure or pulse rate, which can be a distinct advantage with any patient who is likely to develop hypotension. Further, emergence reactions normally are not a problem with patients in the older age group (over 65).



Severely burned patients

Patients with severe burns—and particularly children—are often excellent cases for Ketalar. In children, Ketalar offers rapid surgica anesthesia (generally within three t four minutes) at a range of 9 to 13 mg/kg, with the effect lasting fror 12 to 25 minutes (the time intervals are for IM, not IV). Intramuscular administration avoids the possible difficulty in locating the vein in burr patients (particularly helpful in children where the veins are small) IM administration is also convenien and effective for repeated short-tern anesthesia for such procedures as changing burn dressings, and skin grafts.

advancement in anesthesiology — Ketalar (Ketamine HCl injection) Parke-Davis

Brief summary of prescribing information.

SPECIAL NOTE

EMERGENCE REACTIONS HAVE OCCURRED IN APPROXIMATELY 12% OF PATIENTS.

THE PSYCHOLOGICAL MANIFESTATIONS VARY IN SEVERITY BETWEEN PLEASANT, DREAMLIKE STATES, VIVID IMAGERY, HALLUCINATIONS, AND EMERGENCE DELIRIUM. IN SOME CASES, THESE STATES HAVE BEEN ACCOMPANIED BY CONFUSION, EXCITEMENT, AND IRRATIONAL BEHAVIOR WHICH A FEW PATIENTS RECALL AS AN UNPLEASANT EXPERIENCE. THE DURATION ORDINARILY LASTS NO MORE THAN A FEW HOURS; IN A FEW CASES, HOWEVER, RECURRENCES HAVE TAKEN PLACE UP TO 24 HOURS POSTOPERATIVELY. NO RESIDUAL PSYCHOLOGICAL EFFECTS ARE KNOWN TO HAVE RESULTED FROM USE OF KETALAR.

THE INCIDENCE OF THESE EMERGENCE PHENOMENA IS LEAST IN THE YOUNG (15 YEARS OF AGE OR LESS) AND ELDERLY (OVER 65 YEARS OF AGE) PATIENT. ALSO, THEY ARE LESS FREQUENT WHEN THE DRUG IS GIVEN INTRAMUSCULARLY.

THESE REACTIONS MAY BE REDUCED IF VERBAL, TACTILE, AND VISUAL STIMULATION OF THE PATIENT IS MINIMIZED DURING THE RECOVERY PERIOD. THIS DOES NOT PRECLUDE THE MONITORING OF VITAL SIGNS. IN ADDITION, THE USE OF A SMALL HYPNOTIC DOSE OF A SHORT-ACTING OR ULTRASHORT-ACTING BARBITURATE MAY BE REQUIRED TO TERMINATE A SEVERE EMERGENCE REACTION. THE INCIDENCE OF EMERGENCE REACTIONS IS REDUCED AS EXPERIENCE WITH THE DRUG IS GAINED.

WHEN KETALAR IS USED ON AN OUTPATIENT BASIS, THE PATIENT SHOULD NOT BE RELEASED UNTIL RECOVERY FROM ANESTHESIA IS COMPLETE AND THEN SHOULD BE ACCOMPANIED BY A RESPONSIBLE ADULT.

INDICATIONS

Ketalar (ketamine HCl injection) is recommended:

1. as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketalar is best suited for short procedures but it can be used, with additional doses, for longer procedures;

2. for the induction of anesthesia prior to the administration of other general anesthetic agents;

3. to supplement low-potency agents, such as nitrous oxide.

CONTRAINDICATIONS

Ketamine hydrochloride is contraindicated in those in whom a significant elevation of blood pressure would constitute a serious hazard and those who have shown hypersensitivity to the drug.

WARNINGS

1. Ketalar should be used by or under the direction of physicians experienced in administering general anesthetics and in maintenance of an airway and in the control of respiration.

2. Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.

3. Barbiturates and Ketalar, being chemically incompatible because of precipitate formation, *should not* be injected from the same syringe.

4. Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketalar.

5. Postoperative confusional states may occur during the recovery period.

6. Respiratory depression may occur with overdosage or too rapid a rate of administration of Ketalar, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

Usage in Pregnancy

Since the safe use in pregnancy, including obstetrics (either vaginal or abdominal delivery), has not been established, such use is not recommended.

PRECAUTIONS

1. Because pharyngeal and laryngeal reflexes are usually active, Ketalar (ketamine HCl injection) should not be used alone in surgery or diagnostic procedures of the pharynx, larynx, or bronchial tree. Mechanical stimulation of the pharynx should be avoided, whenever possible, if Ketalar is used alone. Muscle relaxants, with proper attention to respiration may be required in both of these instances.

2. Resuscitative equipment should be ready for use.

3. ***The incidence of emergence reactions may be reduced*** if verbal and tactile stimulation of the patient is minimized during the recovery period. This does not preclude the monitoring of vital signs (see Special Note).

4. The intravenous dose should be administered over a period of 60 seconds. More rapid administration may result in respiratory depression or apnea and enhanced pressor response.

5. In surgical procedures involving visceral pain pathways, Ketalar should be supplemented with an agent which obtunds visceral pain.

6. Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient.

7. An increase in cerebrospinal fluid pressure has been reported following administration of ketamine hydrochloride. Use with extreme caution in patients with preanesthetic elevated cerebrospinal fluid pressure.

ADVERSE REACTIONS

Cardiovascular: Blood pressure and pulse rate are frequently elevated following administration of Ketalar. However, hypotension

(ketamine HCl inj) . . . and a caution



Manipulative diagnostic procedure

Ketalar facilitates diagnostic procedures in which the patient must be moved freely, and in which the maintenance of unaided respiration is essential. The pneumoencephalogram is an example. Once anesthesia is established, the patient can be transferred from a supine to an upright, supported position with ease since Ketalar maintains adequate unaided respiration, and there is minimal relaxation of the skeletal muscles.



Emergency room treatment

A good case for Ketalar can be made for use in accident victims with unknown medical histories brought to the emergency room. In the absence of positive medical history, Ketalar can be a useful agent because of its wide margin of safety. Consideration should be given to the effects of a significant increase in blood pressure, hypersensitivity to the drug, and an elevation in cerebrospinal fluid pressure. Ketalar also provides the benefit of rapid onset, and decreases the chance of aspiration because of active laryngeal-pharyngeal reflexes.



A caution:

Caution should be exercised when administering Ketalar to patients who are known to be alcoholics or who are acutely alcohol-intoxicated as such patients may be prone to untoward reactions.

---

and bradycardia have been observed. Arrhythmia has also occurred.

Respiration: Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of Ketalar (ketamine HCl injection). Laryngospasms and other forms of airway obstruction have occurred during Ketalar anesthesia.

Eye: Diplopia and nystagmus have been noted following Ketalar administration. It also may cause a slight elevation in intraocular pressure measurement.

Psychological: (See Special Note).

Neurological: In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements sometimes resembling seizures (see Dosage and Administration).

Gastrointestinal: Anorexia, nausea and vomiting have been observed; however this is not usually severe and allows the great majority of patients to take liquids by mouth shortly after regaining consciousness (see Dosage and Administration).

General: Local pain and exanthema at the injection site have infrequently been reported. Transient erythema and/or morbilliform rash have also been reported.

DOSAGE AND ADMINISTRATION

Preoperative Preparations:

1. While vomiting has been reported following Ketalar administration, airway protection is usually afforded because of active laryngeal-pharyngeal reflexes. However, since these reflexes may also be diminished by supplementary anesthetics or muscle relaxants, the possibility of aspiration must be considered. Ketalar is recommended for use in the patient whose stomach is not empty when, in the judgment of the practitioner, the benefits of the drug outweigh the possible risks.

2. Atropine, scopolamine, or other drying agent should be given at an appropriate interval prior to induction.

Dosage

As with other general anesthetic agents, the individual response to Ketalar (ketamine HCl injection) is somewhat varied depending on the dose, route of administration, and age of patient, so that dosage recommendation cannot be absolutely fixed. The drug should be titrated against the patient's requirements.

Onset and Duration:

Because of rapid induction following the initial intravenous injection, the patient should be in a supported position during administration.

The onset of action of Ketalar (ketamine HCl injection) is rapid; an intravenous dose of 2 mg/kg (1 mg/lb) of body weight usually produces surgical anesthesia within 30 seconds after injection, with the anesthetic effect usually lasting five to ten minutes. If a longer effect is desired, additional increments can be administered intravenously or intramuscularly to maintain anesthesia without producing significant cumulative effects.

Intramuscular doses, from experience primarily in children, in a range of 9 to 13 mg/kg (4 to 6 mg/lb) usually produce surgical anesthesia within three to four minutes following injection, with the anesthetic effect usually lasting 12 to 25 minutes.

Induction:

Intravenous Route: The initial dose of Ketalar administered intravenously may range from 1 mg/kg to 4.5 mg/kg (0.5 to 2 mg/lb). The average amount required to produce five to ten minutes of surgical anesthesia has been 2 mg/kg (1 mg/lb).

NOTE: The 100 mg/ml concentration (S-V 1585) of Ketalar, *should not* be injected intravenously without proper dilution. It is recommended the drug be diluted with an equal volume of either Sterile Water for Injection, USP, Normal Saline, or 5% Dextrose in Water.

Rate of Administration: It is recommended that Ketalar be administered slowly (over a period of 60 seconds). More rapid administration may result in respiratory depression and enhanced pressor response.

Intramuscular Route: The initial dose of Ketalar administered intramuscularly may range from 6.5 to 13 mg/kg (3 to 6 mg/lb). A dose of 10 mg/kg (5 mg/lb) will usually produce 12 to 25 minutes of surgical anesthesia.

Maintenance of Anesthesia:

Increments of one half to the full induction dose may be repeated as needed for maintenance of anesthesia. However, it should be noted that purposeless and tonic-clonic movements of extremities may occur during the course of anesthesia. These movements do not imply a light plane and are not indicative of the need for additional doses of the anesthetic.

It should be recognized that the larger the total dose of Ketalar (ketamine HCl injection) administered, the longer will be the time to complete recovery.

Supplementary Agents:

Ketalar is clinically compatible with the commonly used general and local anesthetic agents when an adequate respiratory exchange is maintained.

HOW SUPPLIED

Ketalar is supplied as the hydrochloride in concentrations equivalent to ketamine base.

NDC 0071-4581-15—Each 50-ml vial contains 10 mg/ml. Supplied in cartons of 10.

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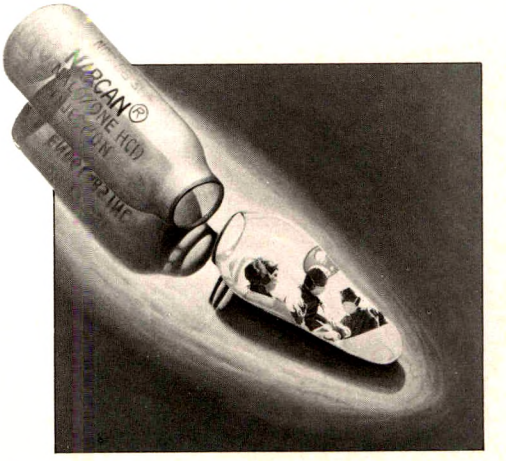
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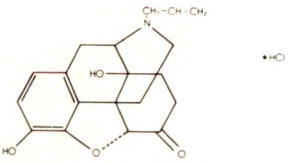
DUPONT

NARCAN® is an Endo registered U.S. trademark; U.S. Pat. 3,254,088.

OF NARCOTIC-SUPPLEMENTED ANESTHESIA

NARCAN®
naloxone HCl

DESCRIPTION NARCAN® (naloxone hydrochloride), a narcotic antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.



NALOXONE HYDROCHLORIDE
(-)-17-Allyl-4, 5α-epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride

Naloxone hydrochloride occurs as slightly off-white crystals, and is soluble in water, slightly soluble in alcohol and practically insoluble in ether.

NARCAN® (naloxone hydrochloride) Injection is available in two concentrations, 0.02 mg and 0.4 mg of naloxone hydrochloride per ml. Each ml of either strength contains 8.6 mg of sodium chloride; and 2.0 mg of methylparaben and propylparaben as preservatives in a ratio of 9 to 1. pH is adjusted with hydrochloric acid.

ACTIONS NARCAN® (naloxone hydrochloride) is an essentially pure narcotic antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other narcotic antagonists; NARCAN® (naloxone hydrochloride) does not produce respiratory depression, psychotomimetic effects or pupillary constriction. In the absence of narcotics or agonistic effects of other narcotic antagonists it exhibits essentially no pharmacologic activity.

In the presence of physical dependence on narcotics NARCAN® (naloxone hydrochloride) will produce withdrawal symptoms; it has not been shown to produce tolerance nor to cause physical or psychological dependence.

When NARCAN® (naloxone hydrochloride) is administered intravenously the onset of action is generally apparent within two minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration of NARCAN® (naloxone hydrochloride). Intramuscular administration produces a more prolonged effect than intravenous administration. The requirement for repeat doses of NARCAN® (naloxone hydrochloride), however, will also be dependent upon the amount, type and route of administration of the narcotic being antagonized.

INDICATIONS NARCAN® (naloxone hydrochloride) is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by natural and synthetic narcotics, propoxyphene and the narcotic-antagonist analgesic pentazocine. NARCAN® (naloxone hydrochloride) is also indicated for the diagnosis of suspected acute opiate overdosage.

CONTRAINDICATIONS NARCAN® (naloxone hydrochloride) is contraindicated in patients known to be hypersensitive to it.

WARNINGS NARCAN® (naloxone hydrochloride) should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

The patient who has satisfactorily responded to NARCAN® (naloxone hydrochloride) should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride).

NARCAN®, (naloxone hydrochloride) is not effective against respiratory depression due to non-opioid drugs.

Usage in Pregnancy Safe use of NARCAN® (naloxone hydrochloride) during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or other embryotoxic effects (See ANIMAL PHARMACOLOGY AND TOXICOLOGY). However, NARCAN® (naloxone hydrochloride) should be administered to pregnant patients only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS In addition to NARCAN® (naloxone hydrochloride), other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning.

In an isolated report two patients with pre-existing ventricular irritability requiring lidocaine, and either isoproterenol or epinephrine for hypotension following cardiopulmonary bypass procedures, developed ventricular tachycardia or fibrillation when given NARCAN® (naloxone hydrochloride) I.V. at 9 and 14 hours, respectively, postoperatively for persistent unresponsiveness. Although a direct cause and effect relationship has not been established, NARCAN® (naloxone hydrochloride) should be used with caution in patients with cardiac irritability.

ADVERSE REACTIONS In rare instances nausea and vomiting have been reported in postoperative patients receiving NARCAN® (naloxone hydrochloride) in doses higher than that recommended; a cause and effect relationship has not been established.

DOSAGE AND ADMINISTRATION NARCAN® (naloxone hydrochloride) may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of NARCAN® (naloxone hydrochloride) the patient should be kept under continued surveillance and repeated doses of NARCAN® (naloxone hydrochloride) should be administered, as necessary.

USAGE IN ADULTS Narcotic Overdose—Known or Suspected The usual initial adult dose is 0.4 mg (1 ml) NARCAN® (naloxone hydrochloride) administered I.V., I.M. or S.C. If the desired degree of counteraction and improvement in respiratory function is not obtained immediately following I.V. administration, it may be repeated intravenously at 2 to 3 minute intervals. Failure to obtain significant improvement after 2 or 3 doses suggests that the condition may be due partly or completely to other disease processes or non-opioid drugs.

Post Operative Narcotic Depression For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of NARCAN® (naloxone hydrochloride) are usually sufficient. The dose of NARCAN® (naloxone hydrochloride) should be titrated according to the patient's response. Excessive dosage of NARCAN® (naloxone hydrochloride) may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or tachycardia.

For the initial reversal of respiratory depression, NARCAN® (naloxone hydrochloride) should be injected in increments of 0.1 to 0.2 mg intravenously at two to three minute intervals to the desired degree of reversal i.e., adequate ventilation and alertness without significant pain or discomfort.

Repeat doses of NARCAN® (naloxone hydrochloride) may be required within one to two hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

USAGE IN CHILDREN Narcotic Overdose—Known or Suspected The usual initial child dose is 0.01 mg/kg body weight given I.V., I.M. or S.C. This dose may be repeated in accordance with the adult administration guideline. If necessary, NARCAN® (naloxone hydrochloride) can be diluted with sterile water for injection.

USAGE IN NEONATES Narcotic-induced depression The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M. or S.C. This dose may be repeated in accordance with adult administration guidelines.

HOW SUPPLIED 0.4 mg/ml of NARCAN® (naloxone hydrochloride) for intravenous, intramuscular and subcutaneous administration.

Available in 1 ml ampuls in boxes of 10 and 100.

0.02 mg/ml of NARCAN® (naloxone hydrochloride) NEONATAL INJECTION for intravenous, intramuscular and subcutaneous administration.

Available in 2 ml ampuls in boxes of 10 and 100 ampuls.

ANIMAL PHARMACOLOGY AND TOXICOLOGY In the mouse and rat the intravenous LD_{50} is 150 ± 5 mg/kg and 109 ± 4 mg/kg respectively. In acute subcutaneous toxicity studies in newborn rats the LD_{50} (95% CL) is 260 (228-296) mg/kg. Subcutaneous injection of 100 mg/kg/day in rats for 3 weeks produced only transient salivation and partial ptosis following injections; no toxic effects were seen at 10 mg/kg/day for 3 weeks.

Reproductive studies including fertility, general reproductive performance, embryotoxicity, teratogenicity, and lactation did not show any abnormality in mice and rats at 10 mg/kg/day.

Endo Laboratories, Inc.
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

DUPONT

EDO-050N

May, 1977

ANTILIRIUM

(Physostigmine Salicylate)

TO REVERSE THE TOXIC EFFECTS UPON THE CENTRAL NERVOUS SYSTEM CAUSED BY DRUGS IN CLINICAL OR TOXIC DOSAGES CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING.

DRUGS AND CHEMICALS CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING:

- AMITRIPTYLINE (Elavil, Triavil, Etrafon)
- ANISOTROPINE METHYLBROMIDE
- ATROPINE
- BELLADONNA
- BENACTYZINE
- CHLORPHENIRAMINE
- CYCLOPENTOLATE
- DESIPRAMINE (Norpramin, Pertofrane)
- DICYCLOMINE
- DIPHENHYDRAMINE
- DOXEPIN (Sinequan)
- HOMATROPINE
- HYOSCINE
- HYOSCYAMUS
- IMIPRAMINE (Tofranil, Presamine)
- ISOPROPAMIDE
- MEPENZOLATE
- METHANTHELINE
- METHAPYRILENE
- NORTRIPTYLINE (Aventyl)
- PIPENZOLATE BROMIDE (Piptal)
- PROPANTHELINE
- PROTRIPTYLINE (Vivactil)
- PYRILAMINE
- SCOPOLAMINE
- STRAMONIUM
- PHENOTHIAZINES
- TRICYCLIC ANTIDEPRESSANTS (Aventyl, Elavil, Etrafon, Norpramin, Pertofrane, Presamine, Tofranil, Triavil, Vivactil)
- THIORIDAZINE (Mellaril)

INDICATIONS: TO REVERSE THE TOXIC EFFECTS UPON THE CENTRAL NERVOUS SYSTEM CAUSED BY DRUGS IN CLINICAL OR TOXIC DOSAGES CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING.

SEVERE ANTICHOLINERGIC POISONING MAY PRODUCE: COMA, MEDULLARY PARALYSIS AND DEATH.

CENTRAL TOXIC EFFECTS MAY INCLUDE: HALLUCINATIONS, DELIRIUM, DISORIENTATION, ANXIETY AND HYPERACTIVITY.

Before prescribing, please consult complete product information, a summary of which follows:

ACTION: ANTILIRIUM (physostigmine salicylate) is a salicylic acid derivative of an alkaloid extracted from seeds of Physostigma Venenosum (calabar bean). The action of the parasympathetic nerves is intermediated by the formation of acetylcholine at the peripheral end of these nerves. Physostigmine inhibits the destructive action of cholinesterase and thereby prolongs and exaggerates the effect of the acetylcholine.

Physostigmine contains a tertiary amine and easily crosses the blood brain barrier, while neostigmine contains a quaternary amine and is not capable of crossing the structure. This may explain why neostigmine does not cause reversal of anticholinergic-induced delirium while physostigmine does.

Dramatic reversal within minutes of coma, hallucinations, and other signs can be expected if the diagnosis is correct and the patient has not suffered anoxia or other insult. Therapeutic doses may be necessary at intervals as life-threatening signs recur. Physostigmine is destroyed in the body in 60 to 120 minutes.

CONTRAINDICATIONS: Physostigmine should not be used in the presence of asthma, gangrene, diabetes, cardiovascular disease, mechanical obstruction of the intestines or urogenital tract or any vagotonic state, and in patients receiving choline esters or depolarizing neuromuscular blocking agents.

WARNING: If excessive symptoms of salivation, emesis, urination and defecation occur, the use of ANTILIRIUM should be terminated. If excessive sweating or nausea occur, the dosage should be reduced.

Intravenous administration should be at a slow, controlled rate, no more than 1 mg. per minute (see dosage). Rapid administration can cause bradycardia, hypersalivation leading to respiratory difficulties and possibly convulsions.

An overdosage of ANTILIRIUM can cause a cholinergic crisis.

PRECAUTIONS: Because of the possibility of hypersensitivity in an occasional patient, atropine sulfate injection should always be at hand since it is an antagonist and antidote for physostigmine.

ADMINISTRATION AND DOSAGE: The usual adult dose of ANTILIRIUM is 0.5 to 2.0 mg. intramuscularly or intravenously. Intravenous administration should be at a slow, controlled rate of no more than 1 mg. per minute. It may be necessary to repeat dosages of 1 mg. to 4 mg. at intervals as life threatening signs such as arrhythmias, convulsions and deep coma recur.

IN ALL CASES OF POISONING, THE USUAL SUPPORTIVE MEASURES SHOULD BE UNDERTAKEN.

SUPPLIED: 2 ml. ampules containing: PHYSOSTIGMINE SALICYLATE 1 mg. per ml. Packed 12 ampules per box.

NDC 0456-1037-12

CAUTION: Federal law prohibits dispensing without prescription.

REFERENCES:

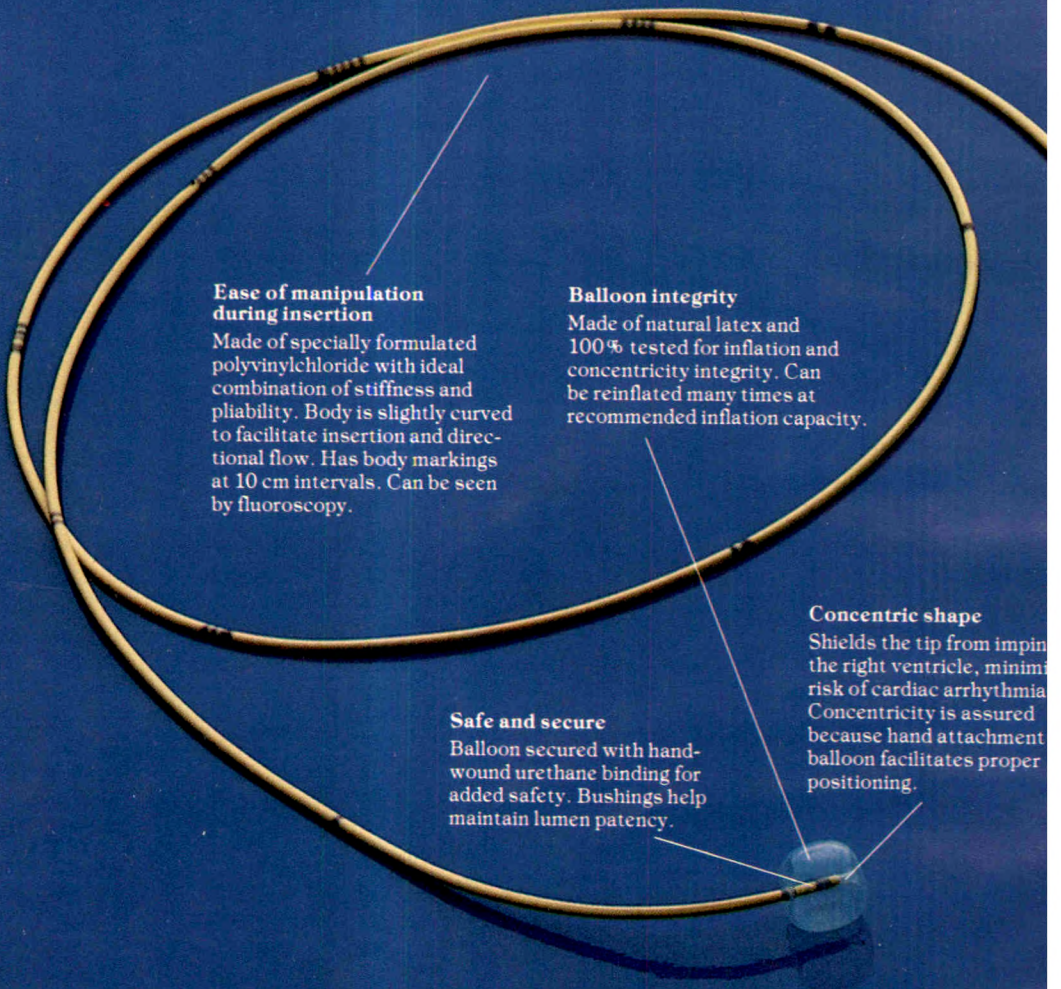
Greene, L. T.: Physostigmine treatment of anticholinergic drug depression in postoperative patients. Anesth & Analg, March-April 1971; 50-2: 222-226.

Rumack, B.: Anticholinergic poisoning: Treatment with physostigmine. Pediatrics, Sept. 1973.

Slovis, T. L., Ott, J. E., Tietelbaum, D. T., and Lipscomb, W.: Physostigmine therapy in acute tricyclic antidepressant poisoning. Clinical Toxicology, 4:451, 1971.

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What to look for in t



Ease of manipulation during insertion
Made of specially formulated polyvinylchloride with ideal combination of stiffness and pliability. Body is slightly curved to facilitate insertion and directional flow. Has body markings at 10 cm intervals. Can be seen by fluoroscopy.

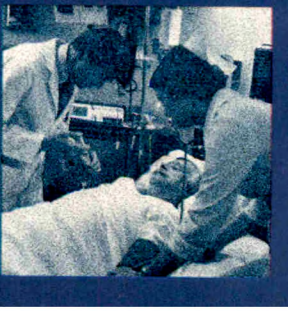
Balloon integrity
Made of natural latex and 100% tested for inflation and concentricity integrity. Can be reinflated many times at recommended inflation capacity.

Concentric shape
Shields the tip from impin the right ventricle, minimi risk of cardiac arrhythmia Concentricity is assured because hand attachment balloon facilitates proper positioning.

Safe and secure
Balloon secured with hand-wound urethane binding for added safety. Bushings help maintain lumen patency.

These are the features that have helped make the Edwards' SWAN-GANZ Catheter from Edwards Laboratories the most widely used in the world. In fact, of all open heart medical teaching centers in the United States, 85% of them routinely use the SWAN-GANZ Catheter for hemodynamic monitoring.

The reasons? More clinical experience (over one-half million inserted), hundreds of published papers in the medical literature, unsurpassed manufacturing quality (15 separate quality control checks meticulous hand-



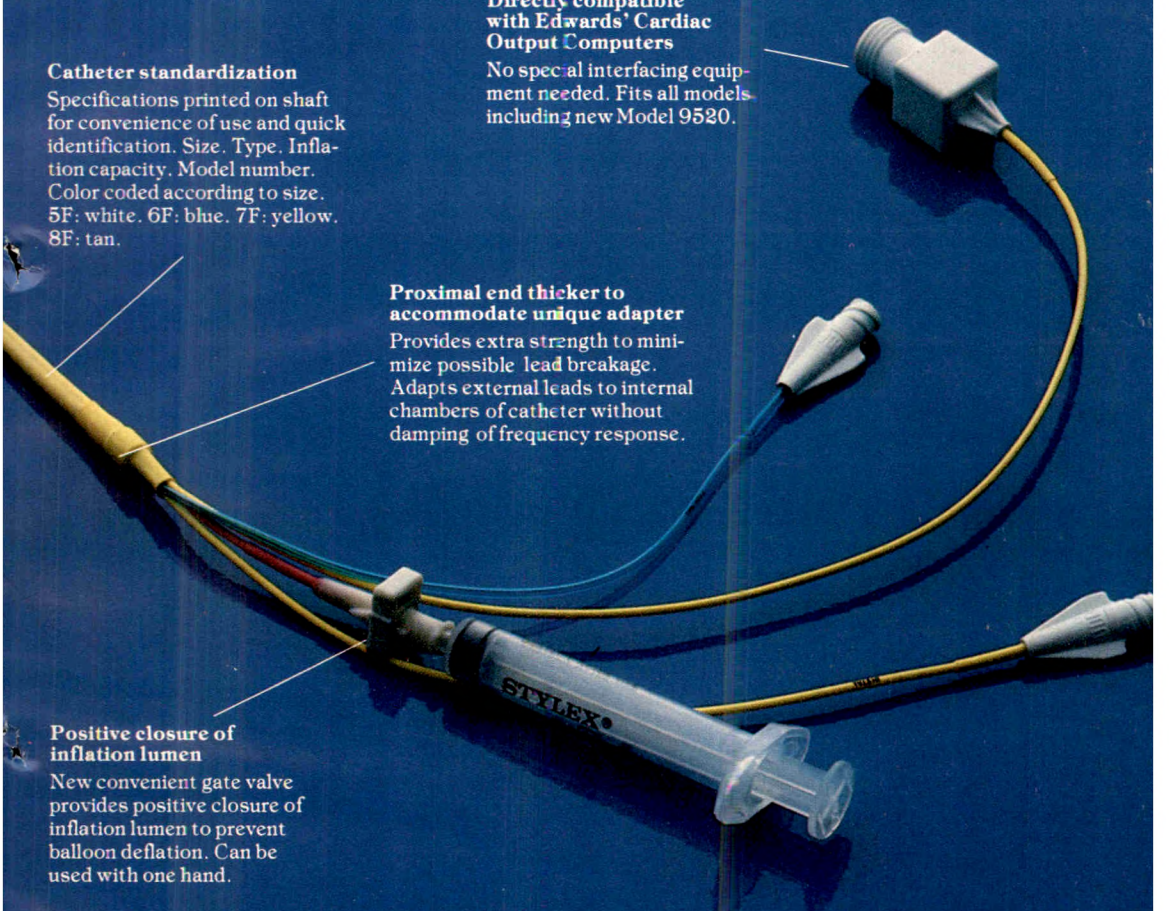
SWAN-GANZ is a registered trademark, Edwards Laboratories.

SWAN-GANZ® Catheter.

Directly compatible with Edwards' Cardiac Output Computers
No special interfacing equipment needed. Fits all models including new Model 9520.

Catheter standardization
Specifications printed on shaft for convenience of use and quick identification. Size. Type. Inflation capacity. Model number. Color coded according to size. 5F: white. 6F: blue. 7F: yellow. 8F: tan.

Proximal end thicker to accommodate unique adapter
Provides extra strength to minimize possible lead breakage. Adapts external leads to internal chambers of catheter without damping of frequency response.



Positive closure of inflation lumen
New convenient gate valve provides positive closure of inflation lumen to prevent balloon deflation. Can be used with one hand.

wound construction, 100% testing, wide selection of catheter types/sizes, and support by a company dedicated to excellence in cardiovascular devices.

A complete description of SWAN-GANZ Catheters, details on insertion, placement and complications are described in journal reprints and technical data available from Edwards.

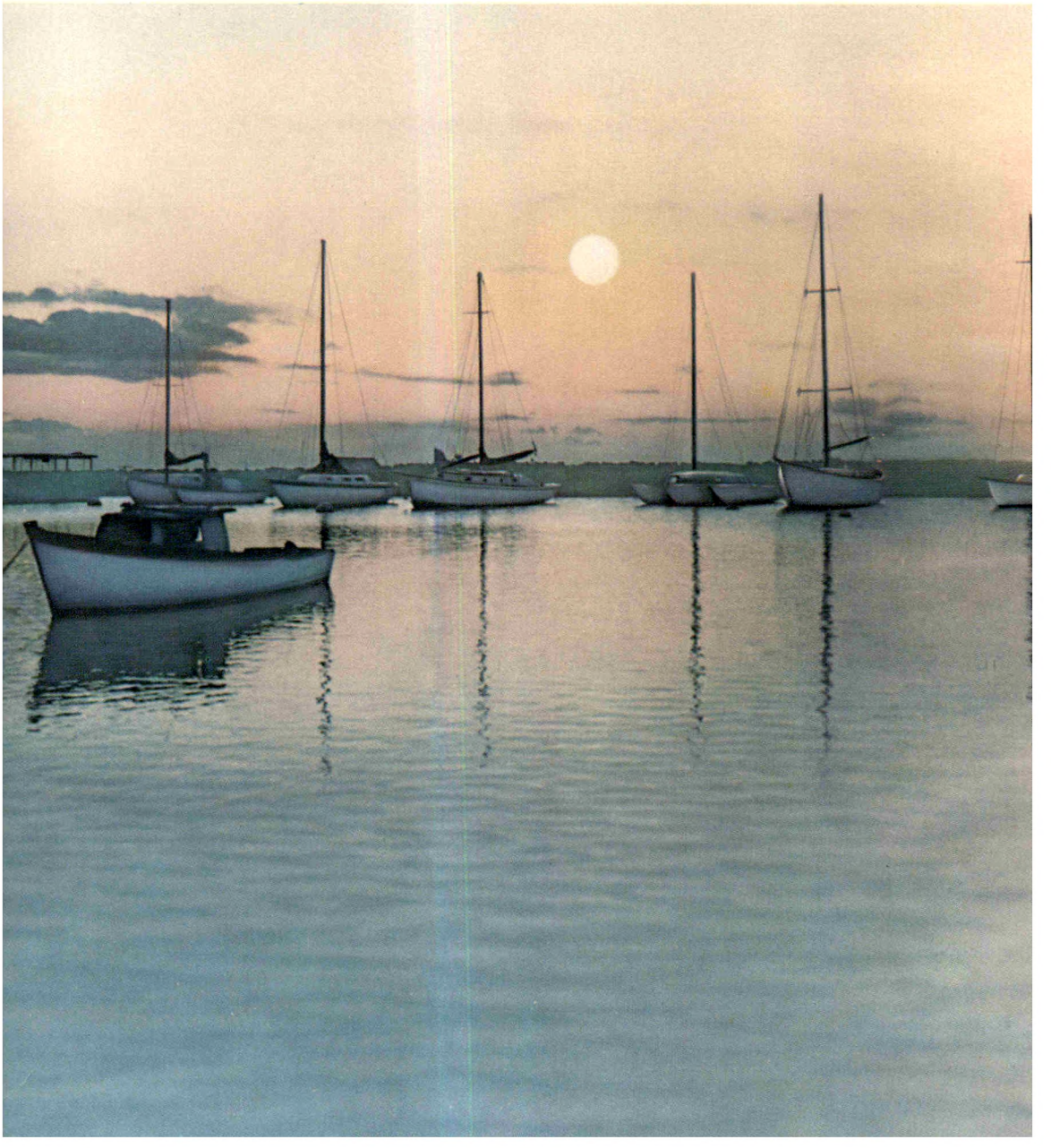
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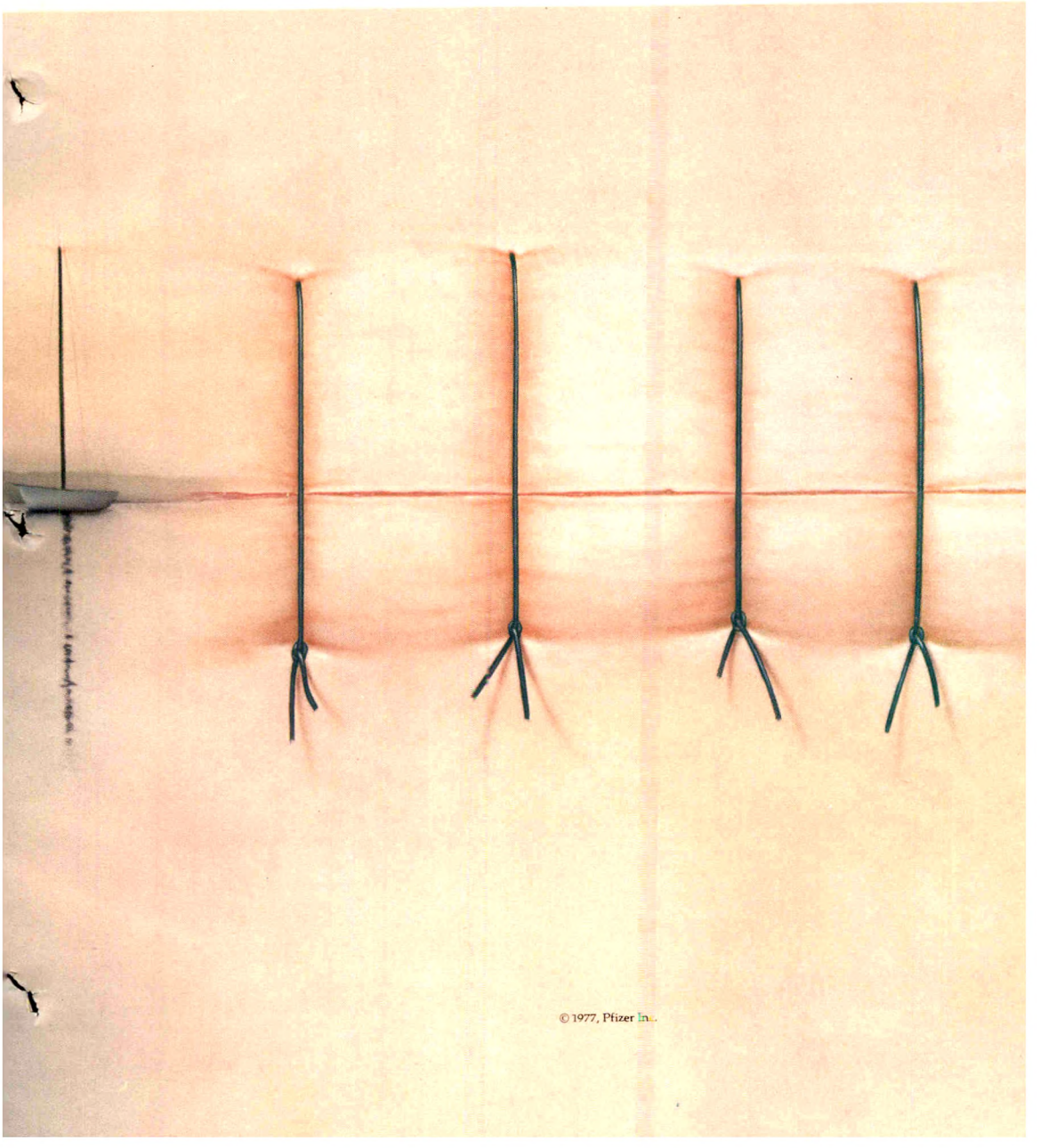


Vistaril® I.M.
(hydroxyzine HCl)

—allays anxiety
—reduces narcotic requirements
—and controls emesis

o surgery

Please see Brief Summary on following page for contraindications, precautions and adverse reactions.



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Vistaril® I.M.
(hydroxyzine HCl)
100 mg/2 ml—50 mg/ml and
25 mg/ml Vials and Isojects®

preoperatively and postoperatively

- **allays presurgical anxiety...allays the anxiety that may heighten the perception of postoperative pain**
- **may enhance the effects of analgesics and reduce narcotic requirements**
- **controls postoperative emesis**
- **vital signs are seldom impaired (Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.)**

BRIEF SUMMARY
VISTARIL® (hydroxyzine hydrochloride) Intramuscular Solution
For Intramuscular Use Only
Contraindications: Hypersensitivity to hydroxyzine. The solution is for intramuscular use only and should not, under any circumstances, be injected subcutaneously, intra-arterially, or intravenously.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Since adequate data are not available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

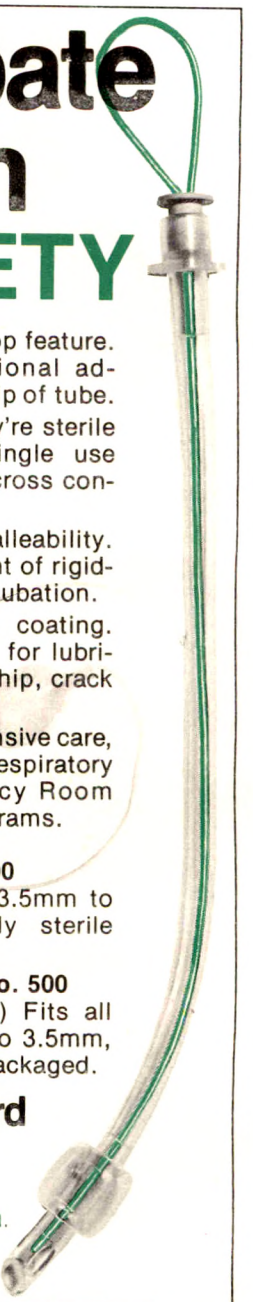
Precautions: HYDROXYZINE MAY POTENTIATE THE ACTION OF CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS AND BARBITURATES. In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. Inadvertent subcutaneous injection may result in significant tissue damage. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-lateral thigh. In children, preferably the mid-lateral muscles of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in order to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid inadvertent intravascular injection.

Adverse Reactions: Drowsiness may occur; if so, it is usually transitory and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with doses considerably higher than those recommended.

Supply: Vistaril (hydroxyzine HCl) Intramuscular Solution: 25 mg/ml—10 ml vials; 50 mg/ml—2 ml and 10 ml vials; Isoject®, 25 mg/ml and 50 mg/ml—1 ml fill; 100 mg/2 ml—2 ml fill.
Military Depot: NSN 6505-00-052-1367 (50 mg/ml, 10 ml vials)
VA Depot: NSN 6505-00-052-1367B (50 mg/ml, 10 ml vials)
More detailed professional information available on request.

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LABORATORIES DIVISION
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- Safe Sureloc™ Stop feature. Prevents unintentional advancement beyond tip of tube.
- Safe because they're sterile and disposable. Single use reduces the risk of cross contamination.
- Safe optimal malleability. Just the right amount of rigidity for quick easy intubation.
- Safe low-friction coating. Eliminates the need for lubrication and will not chip, crack or peel.

Ideal for use in: Intensive care, Anesthesiology, Respiratory Therapy, Emergency Room and Crash Cart Programs.

Adult cat. no. 1000
Fits all tubes from 3.5mm to 10.5mm, individually sterile packaged.
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(Pediatric/Neo-natal) Fits all tubes from 2.0mm to 3.5mm, individually sterile packaged.

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Disposable endotracheal tube guides

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(Dräger Pressure Monitor)

The Drager Pressure Monitor is a breathing system pressure monitor designed to conveniently mount into the circuit of your machine to continually monitor system pressure. The D.P.M. will actuate an audio and visual signal when the maximum pressure amplitude in the system is less than the monitored pressure set at the D.P.M., or when the frequency of artificial ventilation is less than four times per minute.

- *Battery Powered (one 9 volt battery)*
- *Lightweight (1½ lbs)*
- *Compact (2" x 6" x 4½")*
- *Mounting kits available for most anesthesia or ventilator systems*

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NEW

MEDA SONICS

MODEL P81 PROBE AND VERSATONE DOPPLER MODEL D8

Now dramatically reduces interference from electrocautery equipment.

The Model P81 probe is designed to detect venous air embolism during any surgical procedure in which this is a potential complication. This probe and the VERSATONE® Doppler are now manufactured using special shielding techniques to substantially reduce electrocautery interference. This permits the anesthesiologist to continue monitoring Doppler sounds of heart motion even while the electrocautery is being used.

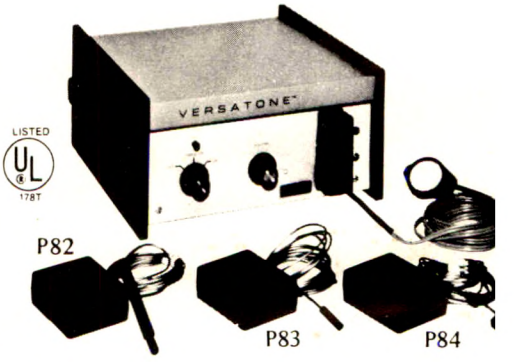
The potential complication of venous air embolism has received considerable recognition in the literature. Michenfelder, et. al.[1], have recommended early diagnosis as the most effective means of preventing serious sequelae from air embolism during neurosurgical procedures performed in the upright position. The Model P81 probe provides a continuous Doppler signal which varies in audible pitch in response to heart and blood flow motion. Distinctive, abrupt changes from the normal sounds are caused by emboli. A tape cassette recording is available on request from MedSonics.

1. Michenfelder, J.D., et. al., "Evaluation of an Ultrasonic Device (Doppler) for the Diagnosis of Venous Air Embolism." Anesthesiology, 36, 2 (February 1972).

CAUTIONS AND CONSIDERATIONS – The ultrasound method of air embolism detection is subject to both false positive and false negative indications. It should not be the only step taken to diagnose venous air embolism.

INTERCHANGEABLE PROBES

The P81 probe is one of a family of probes made for use with the MedSonics VERSATONE® Doppler instruments. It is easily interchangeable with other probes manufactured for this instrument.



P82/P83

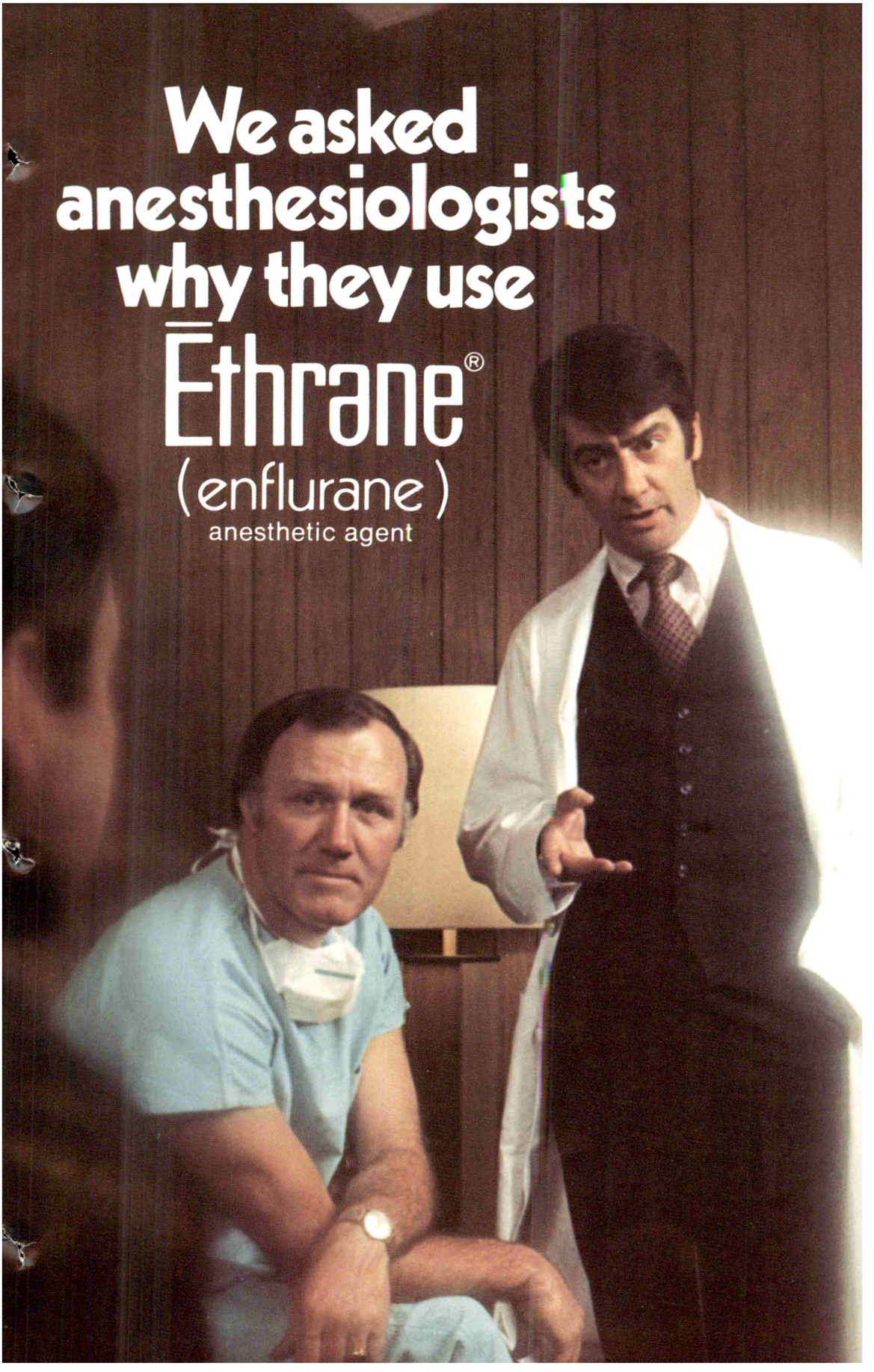
The Model P82 and P83 Doppler ultrasou pencil-shaped probes may be used transcutaneou to detect blood flow or intraoperatively to amine flow in vessels exposed during surgi procedures.

P84

The Model P84 probe is designed for use in mc toring blood flow on the principal blood ves of the arms or legs. It is possible to take syst blood pressures even in hypotensive patients conjunction with a cuff and manometer.

FOR MORE INFORMATION CONTACT

MEDA SONICS MedSonics, Inc.
P.O. Box M (340 Pioneer Way), Mountain View, CA 94(
Toll free telephone: 800 227-8076
In California call collect: (415)965-3333
Telex: 33-4448 Cable: MEDASONICS


We asked anesthesiologists why they use
Ethrane®
(enflurane)
anesthetic agent

"Why do we use Ēthrane® (enflurane)?"

"When you have an anesthetic agent like Ēthrane which you can so predictably control—and it gives you muscle relaxation—that's a real advantage."†

Muscle relaxation with ĒTHRANE (enflurane) usually is sufficient for lower and many upper abdominal procedures at normal levels of anesthesia. Should greater relaxation be required, the ability of ĒTHRANE (enflurane) to potentiate the action of nondepolarizing agents permits significantly reduced dosage of these agents. This property of ĒTHRANE (enflurane) may be particularly useful when supplemental relaxation is required toward the end of surgery.

"When patients wake up following Ēthrane and demonstrate that they have control of their airway, and they have a satisfactory ventilatory exchange, I can send them back to a less controlled environment, with less monitoring, and feel comfortable."†

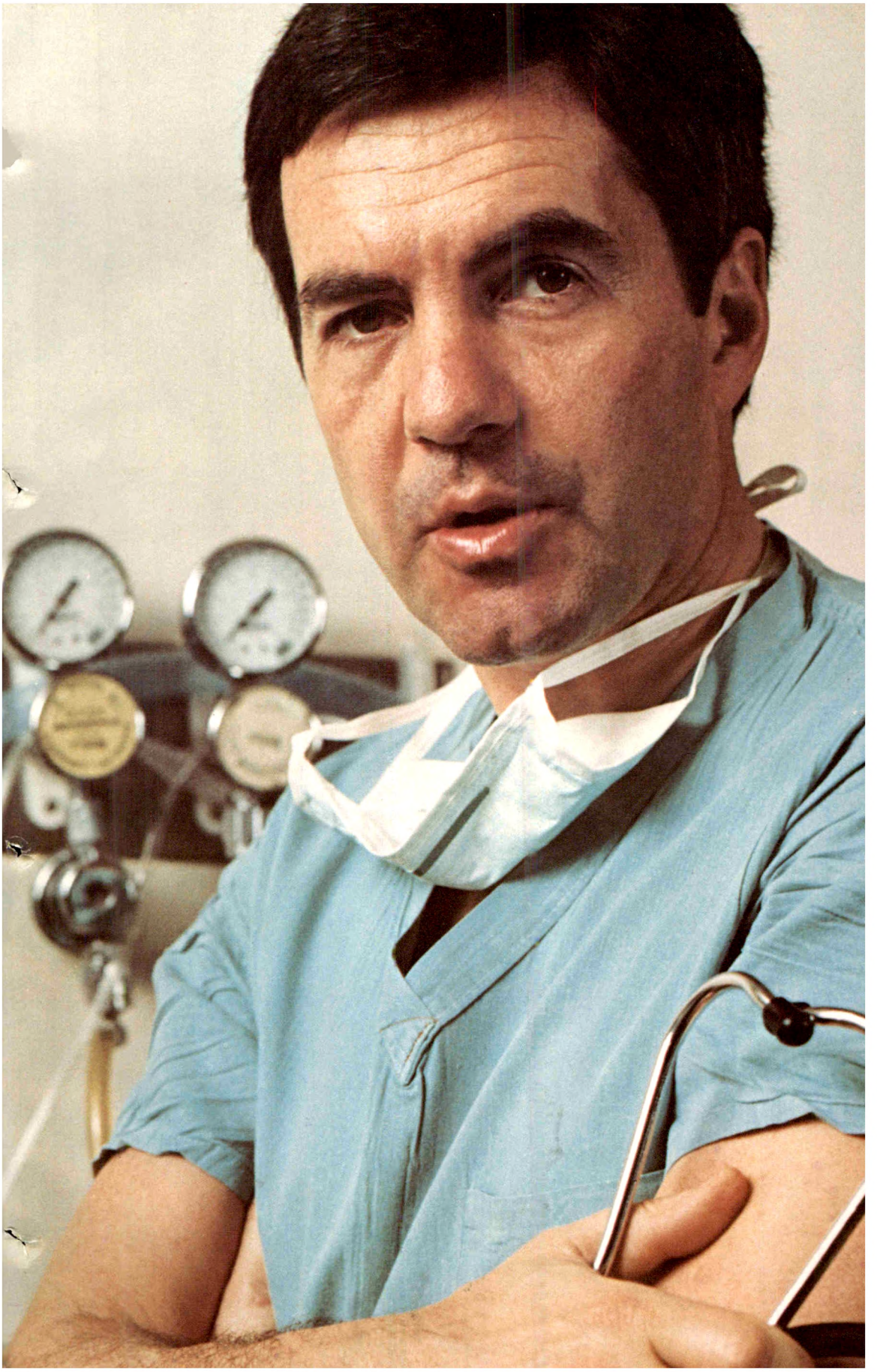
The low blood solubility of ĒTHRANE* (enflurane) provides for its prompt elimination following surgery. Patients usually remain sedated for 10 to 20 minutes, then waken smoothly and rapidly with little or no postanesthetic effect. Vital signs return to preanesthetic levels promptly and patients are generally alert, without nausea and able to take fluids by mouth.

*Blood/gas partition coefficient: 1.9 @ 37°

†Excerpts from taped interview, anesthesiologist in Philadelphia, Pa., on file, Ohio Medical Products.

Please see following page for complete product use information.

Ohio Medical Products

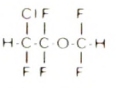


Ethrane® (enflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription

DESCRIPTION

ETHRANE (enflurane) is a nonflammable inhalation anesthetic agent. It is 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether, molecular weight 184.5, and its structural formula is:



The boiling point is 56.5°C at 760 mm Hg, and the vapor pressure (mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C. Vapor pressures can be calculated using the equation:

$$\log_{10}P = A + B/T \qquad A = 7.967$$
$$B = -1678.4$$
$$T = °C + 273.16 \text{ (Kelvin)}$$

The specific gravity (25°/25°C) is 1.517. The refractive index at 20° is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C. The M.A.C. (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70% nitrous oxide and oxygen, and 1.17 in 30% nitrous oxide and oxygen.

ETHRANE is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No chemical stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary to maintain stability even in the presence of ultraviolet light. ETHRANE is stable to strong base and does not decompose in contact with soda lime and does not attack aluminum, tin, brass, iron or copper. The partition coefficients of ETHRANE at 25°C are 74 in conductive rubber and 1.20 in polyvinyl chloride.

ACTIONS

ETHRANE (enflurane) is an inhalation anesthetic. Induction and recovery from anesthesia with ETHRANE are rapid. ETHRANE has a mild, sweet odor. There is mild stimulus to salivation or tracheobronchial secretions when ETHRANE is used alone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia changes rapidly with ETHRANE. ETHRANE reduces ventilation as depth of anesthesia increases. High pCO_2 levels can be obtained at deeper levels of anesthesia if ventilation is not supported. ETHRANE provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during ETHRANE anesthesia. ETHRANE anesthesia has been used in excision of pheochromocytoma in man without ventricular arrhythmias. On the basis of studies in patients anesthetized with ETHRANE and injected with epinephrine containing solutions to achieve hemostasis, up to 10 ml of 1:100,000 or 1:200,000 epinephrine containing solution may be injected subcutaneously at a rate of not more than 10 ml per minute and no more than 30 ml per hour. All customary precautions in the use of vasoconstrictor substances should be observed.

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with ETHRANE. THE NONDEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED. In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height. Neostigmine does not reverse the direct effect of ETHRANE.

Biotransformation of ETHRANE in man results in low levels of serum fluoride ions averaging 15 mM/L. These levels are well below the 50 mM/L threshold level which can produce minimal renal damage in normal subjects; however, it is possible that these levels could result in damage in patients with severely impaired renal function or those undergoing renal transplantation. Depression of lymphocyte transformation does not follow prolonged ETHRANE anesthesia in man in the absence of surgery. Thus ETHRANE does not depress this aspect of the immune response.

INDICATIONS

ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Seizure disorders (see WARNINGS).

Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics.

WARNINGS

Increasing depth of anesthesia with ETHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dom complexes alternating with periods of electrical silence to fla seizure activity. The latter may or may not be associated with mot movement. Motor activity, when encountered, generally consis of twitching or "jerks" of various muscle groups; it is self-limitir and can be terminated by lowering the anesthetic concentratio This electroencephalographic pattern associated with deep ane thesia is exacerbated by low arterial carbon dioxide tension. reduction in ventilation and anesthetic concentration usual suffices to eliminate seizure activity. Cerebral blood flow ar metabolism studies in normal volunteers immediately followir seizure activity show no evidence of cerebral hypoxia. Ment function testing does not reveal any impairment of performanc following prolonged ETHRANE anesthesia associated with or n associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidl only calibrated vaporizers which measure output with reasonab accuracy should be used. Hypotension and respiratory exchang can serve as a guide to anesthesia depth. Deep levels of anesthes may produce marked hypotension and respiratory depression.

The action of nondepolarizing relaxants is augmented b ETHRANE. Less than the usual amounts of these drugs should b used. If the usual amounts of nondepolarizing relaxants are give the time for recovery from myoneural blockade will be longer. the presence of ETHRANE than for other commonly use anesthetics.

Usage in Pregnancy: Safety in pregnancy has not been esta lished. Reproduction studies have been performed in rats ar rabbits, and there is no evidence of harm to the animal fetus. Th relevance of these studies to the human is not known. Since the is no adequate experience in pregnant women who have receive the drug, safety in pregnancy has not been established.

PRECAUTIONS

Bromsulfalein (BSP) retention is mildly elevated postoperative in some cases. This may relate to the effect of surgery since pr longed anesthesia (5 to 7 hours) in human volunteers does n result in BSP elevation. There is some elevation of glucose ar white blood count intraoperatively. Glucose elevation should b considered in diabetic patients. ETHRANE (enflurane) should b used with caution in patients who by virtue of medical or dru history could be considered more susceptible to cortical stimul tion produced by this drug. As with other general anesthetics ar some muscle relaxants, hyperpyrexia has been observed wi the use of ETHRANE.

ADVERSE REACTIONS

1. Motor activity exemplified by movements of various musc groups and/or seizures may be encountered with deep levels ETHRANE (enflurane) anesthesia, or light levels with hypocapni
2. Hypotension and respiratory depression have been reporte
3. Arrhythmias, shivering, nausea, and vomiting have bee reported.
4. Elevation of the white blood count has been observed.

DOSAGE AND ADMINISTRATION

The concentration of ETHRANE (enflurane) being delivered du ing anesthesia from a vaporizer should be known. This may b accomplished by using:

a) vaporizers calibrated specifically for ETHRANE,
b) vaporizers from which delivered flows can easily and readi be calculated.

Nothing is present in the agent to alter calibration or affect th operation characteristics of the vaporizer.

Preanesthetic Medication: Preanesthetic medication should b selected according to the need of the individual patient, takin into account that secretions are weakly stimulated by ETHRAN and the heart rate remains constant. The use of anticholinerg drugs is a matter of choice.

Induction: Induction may be achieved using ETHRANE alon with oxygen or in combination with oxygen-nitrous oxide mixture Under these conditions some excitement may be encountered. excitement is to be avoided, a hypnotic dose of a short-acting ba biturate should be used to induce unconsciousness, followed b the ETHRANE mixture. In general, inspired concentrations 3.5-4.5% ETHRANE produce surgical anesthesia in 7-10 minute

Maintenance: Surgical levels of anesthesia may be obtaine with 1.5-3% ETHRANE. Maintenance concentrations should n exceed 3%. If added relaxation is required, supplemental dose of muscle relaxants may be used. Ventilation to maintain the ter sion of carbon dioxide in arterial blood in the 35-45 mm Hg rang is preferred. Hyperventilation should be avoided in order t minimize possible CNS excitation.

The level of blood pressure during maintenance is an invers function of ETHRANE concentration in the absence of other cor plicating problems. Excessive decreases (unless related to hyp volemia) may be due to depth of anesthesia and in such instance should be corrected by lightening the level of anesthesia.

Overdosage: In the event of overdosage, or what may appe to be overdosage, the following action should be taken:

Stop drug administration; establish that the airway is clear ar initiate assisted or controlled ventilation with pure oxygen a circumstances dictate.

PACKAGING

ETHRANE (enflurane) is packaged in 125 and 250 ml amb colored bottles.

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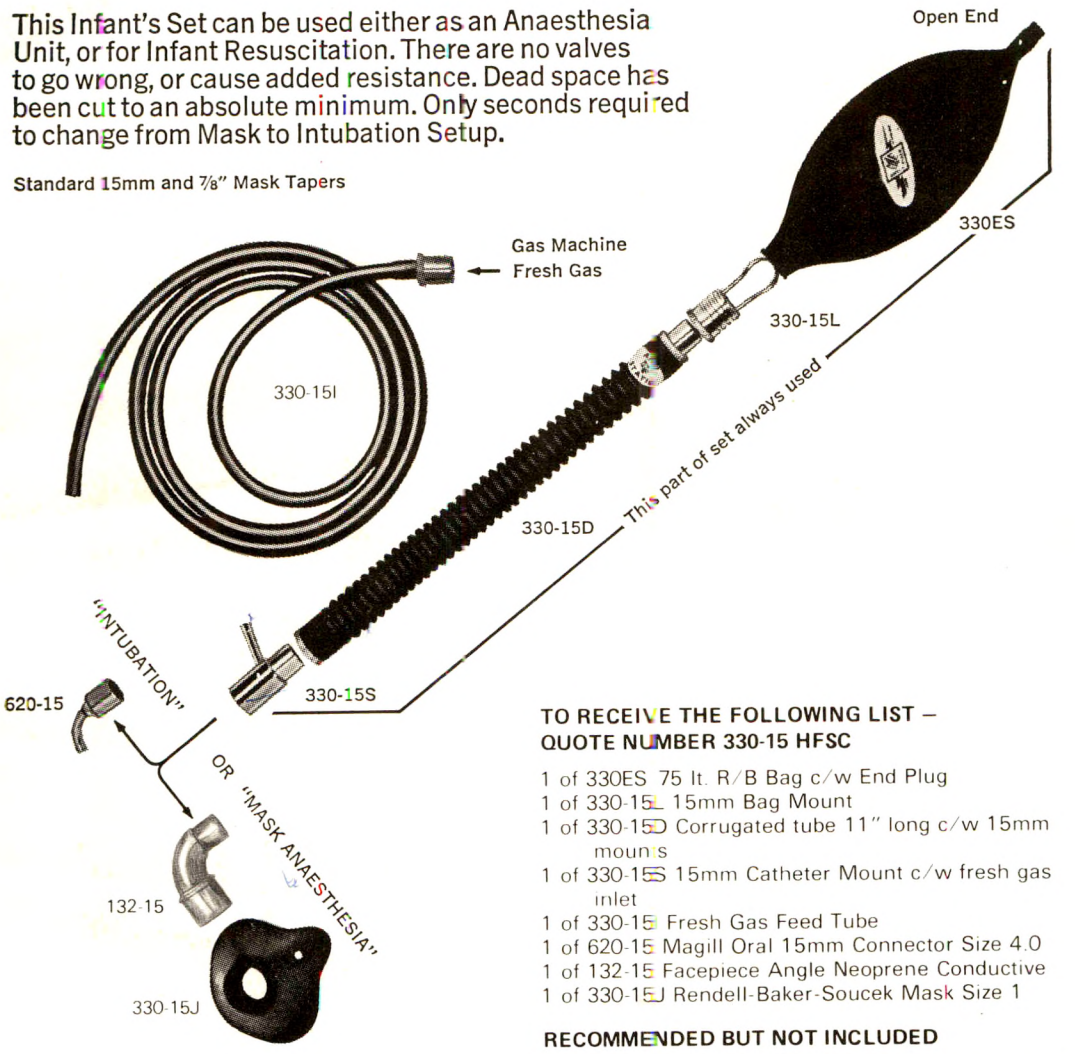
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The Dupaco ORV-1 Ventilator

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IMPORTANT INFORMATION ON THE 52nd CONGRESS

Pre-registration Material, Program, Hotel Card—will be mailed in mid-December to all I.A.R.S. members, associate members, and educational members. (Members outside of U.S., Canada and Mexico who plan to attend, please advise I.A.R.S. Cleveland office by December 1 to assure timely arrival of pre-registration material.)

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Editorial

Gossip and the Acquisition of Knowledge

All men are not created equal when it comes to a desire to learn ever more. Some, driven by a hyperactive intellectual curiosity center hidden somewhere deep in the central nervous system that is constantly depolarizing, spend hours, days, even weeks finding answers to questions, a futile exercise given that each question successfully resolved inevitably gives rise to yet more questions. Others are more relaxed, picking up bits and pieces of new knowledge here and there but not obsessed by a compulsion to remedy their current state of ignorance. Still others apparently could not care less. Untroubled by how much they do not know, they get along one way or another. In most fields of human endeavor these differences in the way we are made up are, with realistic pragmaticism, tacitly accepted as one of the realities of life. That used to be true in medicine, too, but no longer. Today it is mandated that physicians must pursue knowledge throughout their professional careers. If they don't, their license to practice medicine may be in jeopardy, along with their malpractice insurance, their certification by a specialty Board, and even their hospital privileges. This may be a good thing. Only time will tell whether forced marches along the road to knowledge produce the salutary effects on the quality of medical care they are presumed to be associated with. One immediate and obvious result, however, of this recent emphasis on the acquisition of knowledge has been an extraordinary proliferation of continuing education courses designed to enable practicing physicians to learn more and more. Continuing education is today the greatest growth industry in medicine. Greater even than CAT scanners.

A spinoff of all this emphasis on continuing education has been the appearance of belated but nonetheless welcome efforts to define exactly how physicians acquire knowledge. What method of learning is best? Is it through reading of books and journals? Is it through attendance at lectures, seminars, and postgraduate courses? Is it through listening to educational cassettes? Or is it simply through listening to one's peers, the acquisition of knowledge by verbal communication?

The question as to how anesthesiologists acquire knowledge was recently addressed by Fineberg and his associates[1] in an excellent study in which they determined how practicing anesthesiologists acquired knowledge of 3 relatively recent findings in anesthesiology. The 3 findings selected for study were the potential hazards of trace concentrations of anesthetic gases, the effects of diffusion of N_2O into body cavities, and the role of halothane in determining blood loss during therapeutic abortion. The results indicated that journal articles were a major source of information for only the first topic. Continuing education causes were significantly less frequent than were journal articles or communication with colleagues as the means by which knowledge was obtained about all 3 topics. Application of newly acquired knowledge by alteration of clinical practice was effected equally by reading of journals, by attendance at continuing education courses, and by communication with fellow anesthesiologists. Particularly interesting was demonstration of the efficacy of verbal communication with one's peers as a means for both the acquisition of knowledge and for its application to clinical practice.

The importance of communication in the acquisition of knowledge is apparently not limited to anesthesiologists. Lewis Thomas, a well-known and highly regarded basic scientist, finds that much the same phenomenon exists among those with whom he associates.[2] Verbal communication is so effec

tive as a means of transmitting the news about where and how the frontiers of knowledge have been advanced that a corridor conversation in a research institute in Cambridge is reported almost instantaneously in Pasadena, thanks to the telephone, an indispensable scientific instrument in the basic sciences. Gossip is what Thomas calls it. He means it in a friendly way.

The value of gossip as a means for the dissemination of knowledge is great indeed. Of that there can be no question. But before we abandon our reading of journals and before we stop going to lectures and continuing education courses in favor of more casual and considerably more pleasant confabs over a beer or a cup of coffee, we should pause to consider the limitations and pitfalls associated with verbal communication alone as a means for the acquisition of knowledge. The first of these is that both Fineberg et al and Thomas are talking about acquisition of new knowledge. What about old knowledge? New knowledge is important, yes, but so is old knowledge. Real understanding in any biomedical science, clinical or basic, rests more upon knowledge of what has preceded than upon what the latest wrinkle may be. True comprehension is impossible without intimate knowledge of what we already know, fundamental information that can only be dug out by reading the wealth of material published in bygone years, material we have had time to digest and to evaluate. Knowledge about a newly discovered pharmacologic fact about morphine, or a newly discovered use of morphine, for example, is uninterpretable if not downright dangerous if the recipient of this new knowledge is ignorant of what is already known about the pharmacologic actions of morphine and its clinical uses. This essential type of Ursprung knowledge cannot be derived by casual conversations. The true expert knows the literature because he has spent solitary hours going over it, digesting it, and interpreting it, a far cry from the facile practitioner who relies upon casual chit-chat as his source of information. The neophyte entering a new field is particularly in need of firsthand acquaintance with old knowledge. The best place to get this is from books and journals. Continuing education courses and lectures, even when meticulously structured and presented by knowledgeable speakers (neither of which is the invariable rule), can at best supplement the written word. The important study of Fineberg and his colleagues was not designed to evaluate means for acquisition of old knowledge, *real* knowledge, but in view of the essentiality of old knowledge in the practice of medicine one can only hope they will apply their expertise to a study of this, too, in the future.

A second limitation in evaluation of the validity of gossip as a means for the acquisition of knowledge lies in the reality that communication with one's colleagues may transmit accurate new knowledge but in the process may also involve transmission of a great deal of false information. Indeed, the latter would seem to be substantially more frequently the case than the former. In the paper by Fineberg et al, for example, no attempt was made to determine what additional types of information were also being transmitted during verbal communication, other than that concerning 3 selected topics. How much misinformation was transmitted in the course of communication of accurate information? This is important. Communication of inaccurate or false information has the potential for doing more harm than the simultaneous communication of accurate information does good. Anesthesiology, no doubt in common with other clinical disciplines, abounds in old wives' tales and in the initiation and perpetuation of unsubstantiated "knowledge." Fineberg and his associates have done us all a great service in providing us with new insight into the benefits that can be derived by communicating with one's colleagues. One wonders, however, what the results would show if the same technics were also applied to determination of the source of information concerning 3 misconceptions in anesthesiology (finding 3 would prove no problem). What are the relative roles of the printed word, continuing education programs, and communication with one's peers in the genesis and transmission of misinformation? Until such control data are available, it might be well to retain at least a bit of skepticism about gossip as a desirable or even accurate basis for the acquisition of knowledge, new or old.

Nicholas M. Greene, MD

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Sodium Nitroprusside-Induced Hypotension: Effect on Renal Function

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Renal function during induced hypotension produced by infusion of sodium nitroprusside (SNP) was evaluated by measurements of endogenous creatinine clearance and arterial, venous, and bladder urine pH, P_{CO_2}, and P_{O_2} before, during, and after the induction of systemic arterial hypotension in 10 patients undergoing neurosurgical procedures.

Anesthesia was induced with thiopental and was maintained with 0.5 to 1.5% halothane in O_2. Sodium nitroprusside was infused at a rate of 2 to 3 μg/kg/min to decrease mean arterial pressure (MAP) from control values of 90 ± 3 (SEM) torr to 50 ± 2 torr. Anaerobic blood and urine samples were obtained during maintenance of anesthesia but before induced hypotension, during induced hypotension, and 1 hour after restoration of normal MAP. Urine flow was in excess of 1 to 2 ml/min during each sampling period in all patients. Each patient served as his own control.

Endogenous creatinine clearance was significantly decreased ($p<0.05$) from 106 ± 25 ml/min to 41 ± 6 ml/min during hypotension. Clearance values for recovery periods (64 ± 11 ml/min) were not significantly different from control values. We found no significant change in urine P_{O_2}: control values averaged 74 ± 6 torr; during hypotension they averaged 67 ± 3 torr and during recovery 77 ± 5 torr. Arterial and venous P_{CO_2} were lower than urine P_{CO_2} during control, hypotension, and recovery in all patients, a finding which confirmed the absence of gas diffusion across the bladder wall.

The results suggest that medullary renal tissue oxygenation, an index of tissue viability, may have remained adequate despite a significant decrease in endogenous creatinine clearance during the hypotensive period.

Key Words—KIDNEY, function, nitroprusside. ANESTHETIC TECHNICS, induced hypotension. BLOOD PRESSURE, hypotension. ANESTHESIA, volatile, halothane.

ARTERIAL hypotension deliberately induced during anesthesia provides improved operating conditions and reduced blood loss for many surgical procedures.

We were concerned that the kidney, an organ particularly sensitive to ischemia, might be damaged during hypotension.

A number of studies have examined the effect of induced hypotension with sodium nitroprusside (SNP) and trimethaphan (TMP) on renal function. Moraca and coworkers[1] were first to demonstrate radiographically the vasodilator action of SNP on renal blood vessels. Page and associates[2] showed that SNP in both dogs and man lowered renal vascular resistance and perfusion pressure. However, para-aminohippurate and creatinine clearance values were unchanged as was the tubular reabsorptive capacity for glucose. In contrast, Bastron and Kaloyanides[3] studied the protective ef-

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fect of SNP against renal response to systemic hypotension in isolated and intact dog kidneys. They found that a dose of SNP sufficient to reduce mean systemic blood pressure to below 85 torr caused a 10% increase in renal blood flow in the isolated kidney. However, the same degree of hypotension resulted in a marked decrease in renal plasma flow and glomerular filtration rate (GFR), as well as in sodium excretion in the intact kidney. They concluded that SNP, a potent vasodilator, had only a weak renal vasodilating effect and provided no protection against renal ischemia associated with hypotension. These results are consistent with the observation of Kaneko and coworkers[4] who demonstrated an increase in renal venous and systemic venous renin activity in response to acute reductions of arterial pressure by SNP in normotensive and renovascular hypertensive patients. More recently, Wang and coworkers[5] compared the effects of SNP and TMP on the renal hemodynamics in dog. They found that SNP caused no change, whereas TMP caused a decrease in renal blood flow. Leighton and coworkers[6] found an initial decrease in renal blood flow produced by SNP in dogs during halothane anesthesia. Conversely, Pagani and coworkers[7] have recently reported an initial increase in renal blood flow during infusion of SNP in conscious dogs.

The results of previous studies have contradicted one another and, further, may not be applicable to man. No previous attempts have been made to determine which measurement best evaluates changes in renal function during deliberate hypotension, and which correlates best with renal perfusion or oxygenation. Therefore, this study was undertaken to assess the effect of SNP-induced hypotension during halothane-O_2 anesthesia on kidney function and renal oxygenation in man.

METHODS

Ten consenting patients with no known cardiopulmonary or renal diseases undergoing neurosurgical procedures requiring induced hypotension were subjects for this study. The experimental protocol was reviewed and approved by the Institutional Review Board of Northwestern University. Each patient, serving as his own control, underwent the following procedures prior to induction of anesthesia. Two peripheral veins were cannulated and 5% dextrose in lactated Ringer's solution was infused at a rate of 5 to 8 ml/kg/hr. A central venous pressure catheter was inserted via the internal jugular vein. Another catheter was placed in the radial artery to record mean arterial pressure (MAP) with the pressure transducer adjusted to reflect systemic arterial pressure at the level of the surgical field (ie, at the level of the patient's head, about 10 to 15 cm above heart level). Periodic samples from the arterial catheter were taken for blood-gas analysis and chemical determinations.

Anesthesia, without premedication, was induced with thiopental, halothane, and O_2, and the trachea was intubated with the aid of succinylcholine. Anesthesia was maintained with 0.5 to 1.5% halothane in O_2, utilizing a conventional anesthesia circle CO_2 absorption system and controlled ventilation. Mean arterial P_{CO_2} was 31 ± 2 torr during the control period and 35 ± 2 torr during hypotension (see table 2). Electrocardiogram and rectal temperature were monitored, and body temperature was maintained at 36 ± 1 C with a warming blanket.

After induction of anesthesia, a 16-gauge polyethylene catheter equipped with a three-way stopcock was inserted through an indwelling Foley catheter into the urinary bladder for subsequent anaerobic collection of urine. Prior to urine collection, the Foley catheter was clamped distal to the polyethylene catheter. Gentle aspiration of the bladder by a glass syringe attached to the polyethylene catheter was used to keep the bladder empty of urine and to remove trapped air. Bladder contents were aspirated every 5 minutes and pooled for chemical determinations. Urine samples for gas analysis were taken at the end of a study period to give the patient maximal opportunity to equilibrate.

Approximately 30 minutes after induction of anesthesia, a solution of 20% mannitol (1 to 1.5 g/kg) was infused to promote a stable urine output which remained in excess of 1 to 2 ml/min during the procedure. This infusion was continued in most patients throughout the hypotensive period. The patients were allowed to equilibrate with anesthesia for 1 hour, at the end of which time samples of blood and urine were collected for control determinations. During this period, the average control MAP was 90 ± 3 torr. Hypotension, as needed for the specific surgical manipulation, was induced by infusion of SNP (100 μg/ml in 5% dextrose in water) through a minidrop

TABLE 1

Serum Creatinine, Endogenous Creatinine Clearance, and Urinary Po_2 Before, During and After Hypotension Induced by Nitroprusside

Patient	1	2	3	4	5	6	7	8	9	10	Mean ± SEM	Significance
Age	52	31	49	48	55	56	47	22	61	47	47 ± 4	
Body weight (kg)	68	64	70	51	78	73	101	53	67	57	68 ± 5	
Serum creatinine (mg %)												
Control (C)	0.70	0.75	0.95	0.70	0.85	1.10	1.00	0.80	1.00	0.80	0.87 ± .04	
Hypotension (H)	0.70	0.70	1.05	0.70	0.75	0.95	1.20	0.70	1.20	0.80	0.88 ± .07	
Recovery (R)	0.70	0.95	1.05	0.90	0.80	0.90	1.10	1.00	1.00	1.00	0.94 ± .04	
C - H	0.00	−0.05	0.10	0.00	−0.10	−0.15	0.20	−0.10	0.20	0.00	0.01 ± .04	NS
H - R	0.00	0.25	0.00	0.20	0.05	−0.05	−0.10	0.30	−0.20	0.20	0.07 ± .05	NS
C - R	0.00	0.20	0.10	0.20	−0.05	−0.20	0.10	0.20	0.00	0.20	0.08 ± .04	NS
Creatinine clearance (ml/min)												
Control	134	80	69	94	314	106	62	93	32	76	106 ± 25	
Hypotension	52	81	32	62	21	42	31	28	25	31	41 ± 6	
Recovery	85	55	54	130	28	32	110	62	48	35	64 ± 11	
C - H	−72	1	−37	−32	−293	−64	−31	−65	−7	−45	65 ± 26	<0.05
H - R	33	−26	22	68	7	−10	79	34	23	4	23 ± 10	<0.05
C - R	−49	−25	−15	36	−286	−74	48	−31	16	−41	42 ± 30	NS
Urine Po_2 (torr)												
Control	54	88	72	80	57	66	84	113	63	60	74 ± 6	
Hypotension	61	69	67	66	80	73	73	65	64	48	67 ± 3	
Recovery	—	103	72	—	80	63	79	78	83	54	77 ± 5	
C - H	7	−19	−5	−14	23	7	−11	−48	1	−12	7 ± 6	NS
H - R	—	34	5	—	0	−10	6	13	19	6	9 ± 5	NS
C - R	—	15	0	—	23	−3	−5	−35	20	−6	1 ± 7	NS

Two-tailed *t*-tests were performed on differences between paired data.

TABLE 2

Arterial, Venous, and Urinary pH, Pco_2, and Po_2 Before, During, and After Hypotension Induced by Nitroprusside

Patients			Control			Hypotension			Recovery		
No.	Age	Sample	pH	Pco_2 (torr)	Po_2 (torr)	pH	Pco_2 (torr)	Po_2 (torr)	pH	Pco_2 (torr)	Po_2 (torr)
		Arterial	7.43	32	70	7.34	40	107	7.35	39	319
1	52	Venous	7.41	36	48	7.32	44	44	7.32	46	50
		Urine	5.67	58	54	6.13	49	61	6.21*	33*	95*
		Arterial	7.49	25	308	7.49	26	367	7.59	17	349
2	31	Venous	7.51*	24*	35*	7.45	31	69	7.53	21	50
		Urine	6.35	51	88	6.49	53	69	6.90	55	103
		Arterial	7.48	32	220	7.44	34	237	7.48	31	359
3	49	Venous	7.43	39	35	7.45	43	34	7.42	39	37
		Urine	6.04	78	72	6.48	69	67	6.67	65	78
		Arterial	7.61	19	336	7.44	32	388	7.29	36	229
4	48	Venous	7.56	23	56	7.39	36	56	7.26	44	33
		Urine	6.88	70	80	6.32	38	66	—	—	—
		Arterial	7.49	30	192	7.44	34	187	7.36	43	147
5	55	Venous	7.43*	31*	38*	7.39	42	34	7.33	51	41
		Urine	6.96	51	57	6.95	55	80	6.99	72	80
		Arterial	7.47	29	414	7.48	29	427	7.47	30	457
6	56	Venous	7.40	33	42	7.42	33	52	7.41	37	42
		Urine	6.04	58	66	5.69	53	73	6.60	57	63
		Arterial	7.43	29	130	7.33	40	129	7.38	36	309
7	47	Venous	7.36	38	51	7.31	46	37	7.32	44	37
		Urine	5.83	73	84	6.02	61	73	5.77	62	79
		Arterial	7.39	41	365	7.34	47	399	7.33	41	372
8	22	Venous	7.34	54	49	7.29	55	48	7.27	51	42
		Urine	6.15	57	113	5.24	62	65	5.01	47	78
		Arterial	7.52	24	410	7.41	35	379	7.42	37	406
9	61	Venous	7.44	32	29	7.35	43	45	7.37	46	45
		Urine	6.73	42	63	6.04	50	64	5.66	52	83
		Arterial	7.34	44	217	7.45	31	104	7.42	31	278
10	47	Venous	7.33	46	49	7.40	35	27	7.37	36	41
		Urine	6.33	47	60	5.27	52	48	6.25	41	54
Mean ± SEM		Arterial	7.47 ± .02	31 ± 2	266 ± 37	7.41 ± .02	35 ± 2	272 ± 42	7.41 ± .03	34 ± 3	322 ± 28
		Venous	7.41 ± .03	38 ± 3	45 ± 3	7.38 ± .02	41 ± 2	45 ± 4	7.36 ± .02	42 ± 3	42 ± 2
		Urine	6.30 ± .14	59 ± 4	74 ± 6	6.07 ± .20	54 ± 3	67 ± 3	6.23 ± .24	56 ± 4	77 ± 5

*Sample possibly contaminated with air; data not included in calculations

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dispenser at a rate of 2 to 3 μg/kg/min to lower MAP to 50 ± 2 torr. A mean total dose of 12 ± 6 mg of SNP was administered over an average period of hypotension of 111 ± 30 min. Blood and urine samples were taken anaerobically at the end of the hypotensive period as described previously. Mean arterial pressure was allowed to return to normotensive levels by discontinuation of the SNP infusion while continuing halothane-O_2 anesthesia. The blood and urine samples in the recovery period were obtained after blood pressure had stabilized at normotensive levels for at least 1 hour. Mean arterial pressure during the recovery period was 90 ± 5 torr.

Steady-state endogenous creatinine clearance was calculated from blood and urine values obtained during the control, hypotensive, and recovery periods, using the standard Jaffe technic as modified by Chasson.[8] Endogenous creatinine clearance has been widely used in clinical practice as a relatively accurate and reliable measure of glomerular filtration rate.[9] Although the presence of nonspecific chromogens in plasma may cause some variation in measurements, creatinine clearance was employed because of both ease of measurement and accepted accuracy for practical medical purposes.[10] Unlike urea clearance, endogenous creatinine clearance is minimally influenced by urine flow, and serum creatinine concentration is independent of daily dietary protein intake.[11] In this study, the attainment of a steady state and the accuracy of sampling assure maximum validity of the clearance measurement. Our laboratory has a coefficient of variation (SD/mean of 8% for serum creatinine values ranging from 0.6 to 1.7 mg % and a normal range for endogenous creatinine clearance values of 60 to 160 ml/min.

Blood and urine samples for gas analysis were iced and immediately analyzed for pH, P_{CO_2}, P_{O_2}, and H_{CO_3} by standard technics. The data were analyzed for statistical significance using the paired *t*-test.

RESULTS

Table 1 summarizes data on serum creatinine, endogenous creatinine clearance, and urine P_{O_2} before, during, and after SNP-induced hypotension. There were no significant differences in serum creatinine levels before (0.87 ± 0.04), during (0.88 ± 0.07), and after (0.94 ± 0.04) induced hypotension. However, endogenous creatinine clearance was significantly lower ($p<0.05$) during the hypotensive period (41 ± 6 ml/min), as compared to the control (106 ± 25 ml/min) and recovery (64 ± 11 ml/min) periods. Clearance values for control and recovery periods did not differ statistically from each other.

We found no statistical differences in the urine P_{O_2} among control (74 ± 6 torr), hypotensive (67 ± 3 torr), and recovery (77 ± 5 torr) periods.

Urine P_{CO_2} values during control (59 ± 4 torr), hypotensive (54 ± 3 torr), and recovery (56 ± 4 torr) periods were higher than venous and arterial P_{CO_2} values throughout the period of study (table 2). Urine P_{O_2} values during control (74 ± 6 torr), hypotensive (67 ± 3 torr), and recovery (77 ± 5 torr) periods were higher than venous P_{O_2}, but lower than arterial P_{O_2} at all times.

DISCUSSION AND CONCLUSION

Previous studies[11] have shown that hypotension associated with disease states frequently leads to impaired renal function. In contrast, pharmacologically induced hypotension does not appear to be detrimental to renal function, as judged clinically. The purpose of this study was to assess renal function quantitatively in patients requiring induced hypotension during halothane-O_2 anesthesia. It has been shown that urine O_2 tension, when urine flow is adequate, is closely related to medullary blood flow, medullary tissue O_2 tension, sodium reabsorptive capacity, and renal O_2 consumption.[12-17] Hence, renal function was evaluated using endogenous creatinine clearance, and medullary tissue O_2 tension was estimated from changes in bladder urine P_{O_2}.

Our intention was to correlate changes between endogenous creatinine clearance and urine P_{O_2}. We found that P_{O_2} of bladder urine was well maintained even when creatinine clearance was reduced during hypotension. Endogenous creatinine clearance is an index of glomerular filtration rate. Its reduction during the hypotensive period suggests a reduced renal perfusion and is consistent with known hemodynamic responses of renal function. It is well known that the homeostatic responses of the kidney during severe hemorrhagic hypotension result in a shift of blood flow from the outer cortical glomeruli to the juxtamedullary glomeruli.[11] This can be so severe that in

farction of the outer cortex may occur, and yet urine production continues. In the present study, although the blood pressure was lowered from a control value of 90 ± 3 torr to a value of 50 ± 2 torr during hypotension (with an estimated mean renal arterial pressure of 60 torr), the mechanism mediating the hypotension was pharmacologic, not hemorrhagic. The observed changes in endogenous creatinine clearance were probably due to the cardiovascular effects of SNP and not to the anesthesia, since the prehypotensive control and posthypotensive measurements were made during halothane-O_2 anesthesia and without premedicant drugs.

The fact that urine Po_2 remained relatively unchanged during hypotension as compared to control and recovery periods was contrary to our expectation. We anticipated that a reduced renal perfusion during hypotension would reduce O_2 supply to the kidney, thereby reducing medullary tissue O_2 tension and hence urine Po_2. On the contrary, we observed no significant change in urine Po_2 during hypotension. This may suggest a preferential shift of blood supply from cortex to medulla. The fact that urine Po_2 was not decreased, in spite of an approximately 45% drop in MAP, suggests that renal oxygenation was not compromised and that blood flow to the kidney during induced hypotension remained adequate. The urine O_2 tension values observed here correlate well with previous values in normotensive patients receiving 100% O_2.[15] The fact that urine Pco_2 was always greater than that of arterial or venous blood indicates that our urine samples were anaerobic, since exposure to air would result in loss of CO_2. Also, this finding indicates absence of any gas diffusion through the bladder wall.

Finally, we suggest that the measurement of urine O_2 tension may be a useful technic in monitoring patients undergoing hypotensive anesthesia as an indicator of renal medullary oxygenation. Its use to monitor renal cortical oxygenation will require better documentation.

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Histological Evaluation of Cutaneous Wound Healing in Presence of Nitrous Oxide in Rats

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Three-centimetre linear incisions were made in 90 young male Lew/f Mai rats by scalpel through skin to the investing fascia of the left flank. The skin was undermined sharply for a distance of 0.5 cm along both sides of the entire length of the incision. The wound site was closed per primam with Michel clips and left uncovered. Following emergence from anesthesia, rats were randomly allocated to one of three groups of 30 rats each: one group breathed air only and acted as control; the second was exposed to 20% N_2O for 24 hours daily until sacrificed (continuous group); the third was exposed to 20% N_2O for 8 hours daily until sacrificed (intermittent group). Ten rats from each of the three groups were sacrificed after 3, 7, or 10 days postincision. After sacrifice, sections from the wound stained with hematoxylin and eosin or reticulin were examined microscopically.

No histological evidence of an effect on wound healing of skin occurred in rats exposed to 20% N_2O.

Key Words—ANESTHETICS, gases, nitrous oxide. SKIN, wound healing. SURGERY, wound healing.

PROLONGED exposure to N_2O has been cited as toxic to man,[1] laboratory animals,[2,3,4] and tissue culture.[5] Injury has occurred in those tissues which share the property of rapid proliferation. Nevertheless, interest in the nonsurgical use of N_2O has persisted, and N_2O has been applied successfully as an analgesic for the critically ill postoperative patient.[6] Since the surgical wound, too, is a site of rapid proliferation, it is plausible that its healing may be affected adversely by N_2O, thereby increasing risks for the postoperative patient.

In this study we have evaluated the effect of an analgesic concentration of N_2O[7,8] on wound healing by examining in the rat the relationship of the cellular response at the site of surgical injury to the presence of 20% N_2O.

METHODS AND MATERIALS

Under ether anesthesia, 90 young Lew/f Mai rats weighing an average of 125 g were shaved over their left flanks, exposing an area of skin measuring 5 x 4 cm. Following skin cleansing with Povidone-Iodine, a 3-cm linear incision was made by scalpel through skin down to the investing fascia. The skin was undermined by sharp dissection for a distance of 0.5 cm along both sides of the entire incision. The wound was closed per primam with Michel clips and was not cov-

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ered. Following emergence from anesthesia, the rats were randomly allocated to one of three groups of 30 rats each: one group breathed air only and was the control; the second was exposed to 20% N_2O for 24 hours daily until sacrificed (continuous group); the third was exposed to 20% N_2O for 8 hours daily until sacrificed (intermittent group). The rats were exposed in isolation chambers previously described[3] to either air or a mixture of 20% O_2, 20% N_2O, and 60% nitrogen at 24 C, 70% humidity. Both control animals and animals exposed to N_2O were housed in groups of 3 rats per cage and fed standard diets with water ad libitum.

Sacrifice of 10 rats from each of the groups was performed 3, 7, or 10 days following incision by cardiac puncture and exsanguination. After death, the shaved area was excised without disturbing the wound, fixed in cold, neutral 10% formalin for several days, embedded in paraffin, and cut at 5 μm transverse to the long axis of the wound. Tissues obtained from rats sacrificed on the 3rd day were stained with hematoxylin and eosin only. All other tissues were stained with the reticulin stain of Wilder and hematoxylin and eosin.

Tissue sections were evaluated independently by two histologists who were unaware of whether N_2O was used or not. There were no disagreements on their findings.

RESULTS

Rats exposed to N_2O appeared alert and behaved normally. No differences between control rats, breathing air, and rats exposed to N_2O were apparent regarding food and water intake or growth during the 10-day study period.

Wound healing proceeded without incident in 87 of 90 rats. The gross appearance of the healing wound in rats exposed to N_2O was indistinguishable at each time period from the wounds of control rats (fig 1). The three complications were a wound abscess, wound gaping, and a wide scar. Since the complications arose in one rat from each of the three groups, their occurrence was not attributable to the presence of N_2O.

Histological examination also failed to reveal a difference in the progress of healing among the three groups 3, 7, or 10 days following incision. By the 3rd day, the wound site in all three groups was sealed by a fibrin clot which contained inflammatory leukocytic cells, mostly degenerating polymorphonuclear leukocytes (fig 2 and 3). By the 7th day proliferating epithelium had bridged the incised epidermis and thin reticulin staining fibers and fibroblasts had replaced the coagulum (fig 4 and 5). On the 10th day, the cellular layers of the epithelium were identifiable while the incision site in the dermis contained both thin retic-

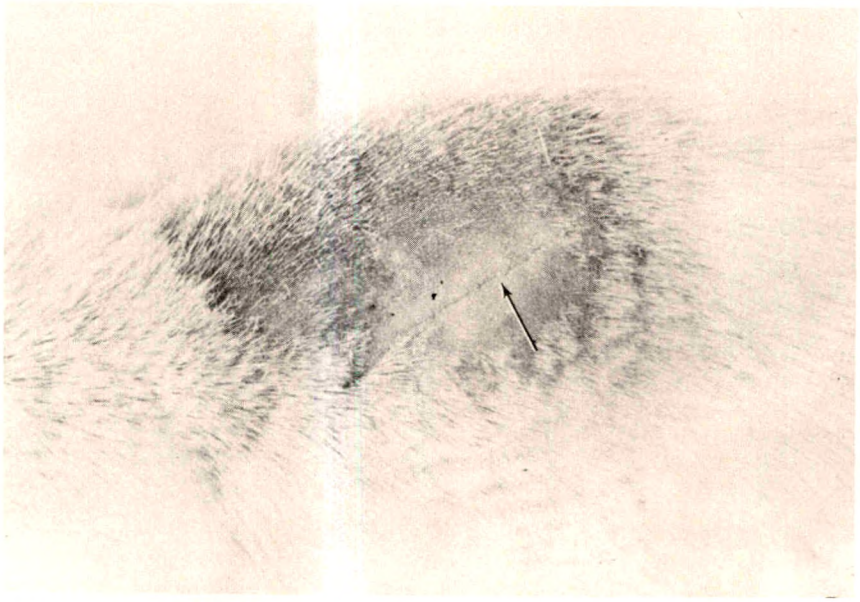


FIG 1. Ten-day-old incision site of rat exposed continuously to 20% N_2O. Note the well-healed wound (arrow).



FIG 2. Three-day-old wound in a control rat. The cut edges of the epidermis (E) and dermis (D), sealed by thin fibrin clot (F), have been separated artifactually. The nuclei (N) of degenerating inflammatory cells are formed within the clot and in the neighboring dermis. Dermal collagen fibers and fibrocytes (C) are noted at the periphery. (H and E stain; × 125)

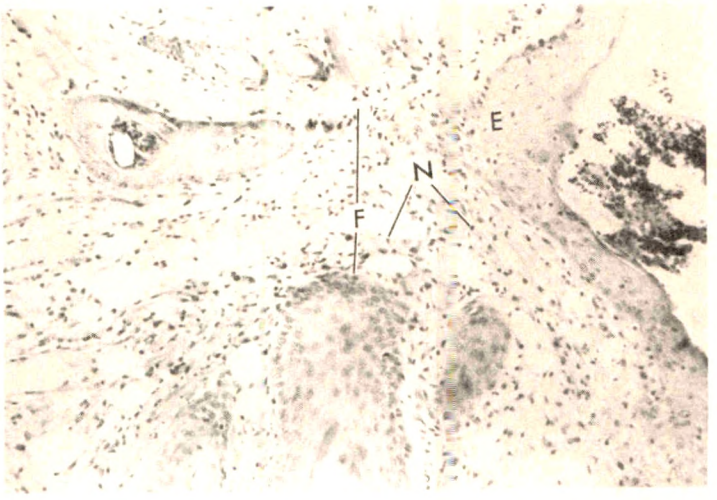


FIG 3. Three-day-old wound from a rat exposed continuously to 20% N_2O. The cleft in the epidermis (E) is out of the field. The fibrin clot (F) is intact and contains inflammatory cells (N). (H and E stain; × 125)

ulin staining fibers and thicker eosinophilic staining fibers, probably young collagen (fig 6 and 7). However, at the wound site the orientation of fibers differed from the surrounding tissue.

DISCUSSION

Prolonged exposure to N_2O is recognized as injurious to rapidly dividing cells. In our rat model (Lew/f Mai), prolonged exposure to 20% N_2O injures both the seminiferous tubule[8] and some hematopoietic tissues, both sites of rapid cellular proliferation. Evidence of toxicity of 20% N_2O was found within 2 days in developing spermatozoa and by 4 days in lymphocytes. The mechanism responsible for the antigrowth action of N_2O remains unclear, although data indicate an effect at two sites during the generation cycle of mammalian cells, during mitosis[9,10] and in S—the DNA synthetic phase.[11] Since cell replication has an important role in healing of both epiderma

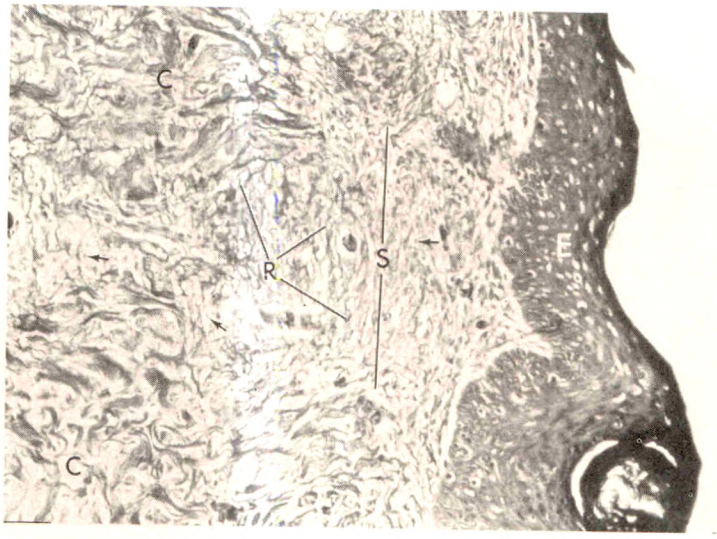


FIG 4. Seven-day-old wound stained with reticulin from a control rat. The epithelium (E) is continuous. The scar site (S) in the dermis contains thin fibers which stain with reticulin and are less eosinophilic than normal collagen with H and E stain. Nuclei of fibroblasts (arrows) are within the interstices of the fibers. (Wilder's reticulin stain; × 125)

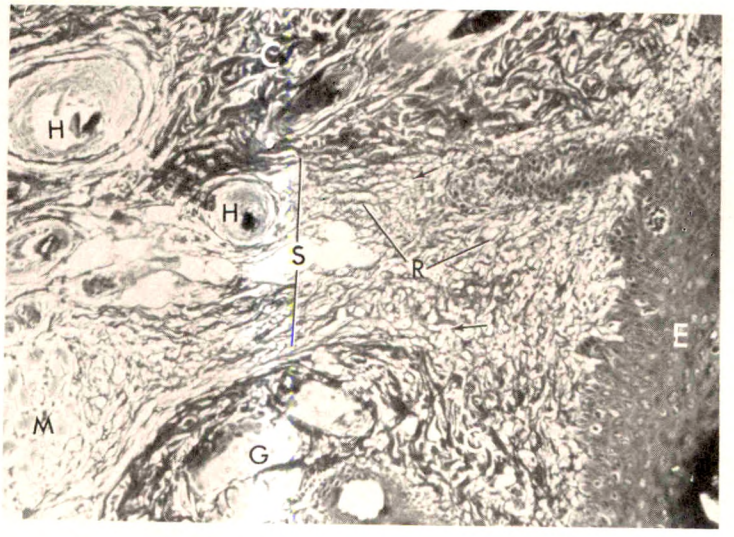


FIG 5. Seven-day-old wound stained with reticulin from rat exposed continuously to 20% N_2O. The epithelium (E) is continuous, and the developing scar (S) is traversed by fine reticulin-stained fibers (R). Arrows indicate fibroblast nuclei in the scar. Normal dermal constituents, such as hair follicles (H) and sebaceous glands (G), are located at the periphery. Necrotic muscle fibers (M) are present. (Wilder's reticulin stain; × 125)

and dermal tissues, it is possible that anesthetic interference with the generation cycle might affect the critical timing of the complex sequences in repair and lead to impaired healing.

Many methods[1,2] have been employed in evaluating wound healing, including studies of morphology with light and electron microscopy, rate of cicatrization, gain in tensile strength, breaking strength, and biochemical analysis for hydroxyproline and mucopolysaccharides. Since we performed only a light microscopic evaluation of the healing wound, our conclusions can only be tentative. Nevertheless, the sequence of histological events in healing surgical wounds has been firmly established. Although one period merges into another, three distinct microscopic phases have been described: (1) the substrate phase (inflammatory, exudative, or lag phase); (2) the proliferative



FIG 6. Ten-day-old wound stained with reticulin from a control rat. Epithelial layers (E) are more identifiable. Scar (S) is well healed and bridged by stouter collagenous (C) fibers. However, the thin reticulin fibers (R) dominate the scar. Fibroblast nuclei (arrows) are seen. (Wilder's reticulin stain; × 125)

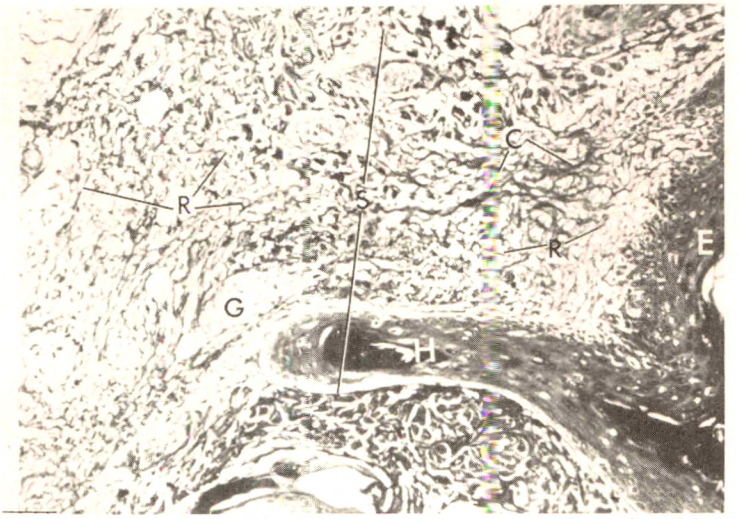


FIG 7. Ten-day-old wound stained with reticulin from a rat exposed continuously to 20% N_2O. Epithelial layers (E) are more identifiable. Well-healed scar (S) contains fine reticulin fibers (R) and stouter collagenous fibers (C). Hair follicle (H) and sebaceous gland (G) are near wound site. (Wilder's reticulin stain; × 125)

phase (connective tissue, fibroblastic phase); and (3) the remodeling phase (resorptive, differentiating phase).[13] The substrate phase extends from wounding to postwound day 4 and is characterized by hemostasis, a vascular exudate, and a leukocytic inflammatory reaction at the wound edge and in the coagulum (fig 2 and 3). The proliferative phase extends from postwound days 5 to 20 and includes epithelialization, wound contraction, capillary endothelial proliferation, and connective-tissue repair. Replication by epithelium and the fibroblast dominates the proliferative period (fig 4 to 7). The remodeling phase begins during the 3rd postwound week and lasts many months. During this period the wound has its major gain in tensile strength.[12]

Our study found that 20% N_2O affected neither the sequential appearance nor function of the different cell types associated with the complicated processes of wound healing through 10 postwound days. It is

established that leukocytes migrate into the coagulum of the wound soon after injury. Their role is to control infection and remove dead cells and debris by phagocytosis. Failure of proper debridement can delay the appearance of the fibroblast and impair the quality of its secretions, especially the collagen.[14,15] Although data are lacking for N_2O, clinically useful concentrations of many volatile anesthetic agents affect leukocytic locomotion.[16] Halothane, the most studied of the anesthetics, depresses the motility of both lymphocytes in vitro[17] and neutrophils responding to an intraperitoneal injection of bacterial endotoxin in mice.[18] Our finding of proper numbers of leukocytes in the incision site on day 3 postwound suggests that 20% N_2O does not significantly impair leukocytic migration in the rat (fig 3).

Our studies indicate that the proliferative phase is well underway on day 7 and that there is no difference in control animals and in animals exposed to 20% N_2O (fig 4 and 5). The presence of N_2O did not result in defective phagocytosis at the wound site, since fibroplasia appears normal (fig 5 and 7). Our findings are supportive of Cullen,[19] who studied the effect of N_2O on phagocytosis and metabolism of human leukocytes in vitro. He reported that 80% N_2O did not inhibit latex particle phagocytosis or nitroblue tetrazolium dye (NBT) reduction.

Wound strength is dependent on collagen, a protein secreted by the fibroblast early in the proliferative period. New collagen deposition in a skin wound of the rat reaches its peak concentration by 7 days and begins to diminish by 35 days postwound.[12] Although extensively studied in the past decade, many aspects of its formation and interactions with ground substances remain unclear. Furthermore, data are lacking regarding the action of anesthetics, including N_2O, on collagen synthesis. Nevertheless, the normal appearance of reticulin on day 7 and the appearance of thicker eosinophilic staining fibers at the wound site on day 10 suggest that 20% N_2O does not impair collagen formation. Parbrook[20] reported that continuous exposure to N_2O, 25 or 60%, for 3 days after wounding affected neither tensile strength nor epithelial coverage of the incision. However, those parameters of wound healing were studied after 3.5 and 6 days, respectively, of air breathing prior to sacrifice. Recently it has been demonstrated that certain of the toxic effects of N_2O are reversed within 3 days of air breathing.[3,4] Although the methodology of Parbrook's experiments appears questionable today, we are nevertheless in agreement with his conclusion that N_2O may not affect wound healing.

One must use caution, however, in extrapolating the results obtained in rats to the problems of wound healing in humans. Although the basic mechanisms appear identical, rates of healing differ not only between species, but also among the various tissues of the same animal.[12] To illustrate, gain in wound strength of skin is only 20 to 30% of preincision strength by 3 weeks after incision while a bladder wound regains its normal strength in the same period.

In summary, introduction of 20% N_2O into the environment of surgically incised rats yielded no morphologically detectable differences in either cell sequence or duration of the processes of healing of cutaneous tissues, which suggests that N_2O may not have an adverse influence on the process of healing of skin.

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LOCAL ANESTHETIC ALLERGY

The clinical histories of 71 patients evaluated for suspected local anesthetic (LA) allergy were reviewed retrospectively. Histories were classified as (1) immediate generalized reactions (15%), (2) localized swelling at the injection site (25%), (3) nonspecific systemic symptoms (42%), and (4) other histories (17%). Serial dilutional intradermal skin tests were performed with mepivacaine, lidocaine, and procaine in 59 patients. Five skin-test-positive patients were found, and each had a positive reaction to a LA to which, by history, they had not reacted. In 50 patients, when a LA was subsequently required, a subcutaneous challenge was performed with a LA chosen for chemical nonsimilarity. No significant reactions were observed in this group. Three patients tolerated a challenge with a LA to which they were skin-test positive. These data indicate (1) the low incidence of a history of reactions compatible with a systemic IgE-mediated mechanism in patients referred for evaluation of LA allergy, (2) the lack of specific and clinically relevant information provided by dilutional skin tests, and (3) the apparent safety and usefulness of careful challenge with an alternative LA. *(Incaudo G, Schatz M, Patterson R, et al: Administration of local anesthetics to patients with a history of prior adverse reaction. J Allergy Clin Immunol 61:339-345, 1978)*

Bupivacaine and Other Amide Local Anesthetics Inhibit the Hydrolysis of Chloroprocaine by Human Serum

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The rate of hydrolysis of chloroprocaine by human serum was studied in the presence and absence of a number of amide local anesthetics and their metabolites. Bupivacaine (2.4 μg/ml) and etidocaine (2.3 μg/ml) caused 38% and 21% inhibition respectively of the rate of chloroprocaine hydrolysis. Circulating concentrations of these drugs have been reported in this range by several investigators following epidural doses of 150 to 400 mg of either drug. Mepivacaine, lidocaine, and two lidocaine metabolites (glycine xylidide and monoethylglycine xylidide) were only inhibitory at levels much greater than those seen in blood following the usual local anesthetic doses of the parent compounds. Since serum is an important site of chloroprocaine metabolism in man, the probability of chloroprocaine intoxication may be increased when it is administered with local anesthetics such as bupivacaine and etidocaine.

Key Words—ANESTHETICS, local, 2-chloroprocaine. ANESTHETICS, local, bupivacaine. ANESTHETICS, local, etidocaine. ANESTHETICS, local, lidocaine. ANESTHETICS, local, mepivacaine. INTERACTIONS, drug, local anesthetics. TOXICITY, local anesthetics.

CONTROVERSY surrounds the use of combinations of local anesthetics to achieve a therapeutic advantage. Although clinically such admixtures are common,[1,2] animal data suggest that synergistic toxicity may result.[3] Since metabolism by serum cholinesterase (E 3.1.1.8) is an important site of detoxification of ester-type local anesthetics,[4] substantial inhibition of this enzyme by coadministered drugs could increase the toxicity of ester anesthetics such as chloroprocaine and hence result in synergistic toxicity. The principal purpose of the present study was to determine if a clinically significant drug-drug interaction is likely between chloroprocaine and amide local anesthetics which are simultaneously employed.

METHODS AND MATERIALS

Venous blood was obtained from healthy normal volunteers (4 males and 3 females)

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following an overnight fast. The subjects had received no medication for at least 7 days prior to blood donation except for one volunteer who had occasionally utilized aluminum hydroxide–alginate–magnesium trisilicate antacid tablets. The blood was allowed to clot at room temperature, and serum was separated, placed in clean tubes, and used within 6 hours or stored at −20 C until used.

The rate of chloroprocaine hydrolysis was measured as the rate of change of absorbance of light (313 nm) with time in a double-beam ultraviolet spectrophotometer.[4] The hydrolysis reaction and its inhibition were studied at 37 C because of its greater physiological significance, though a number of studies performed at 25 C suggested that temperature had little effect on the hydrolytic process or its inhibition. In the experiments examining the effect of concentration of the amide anesthetics upon the rate of chloroprocaine hydrolysis (see fig 1 and 2), the reaction mixture contained 0.2 ml of serum, 0.8 ml of 1/15 *M* sodium dihydrogen phosphate buffer adjusted to pH = 7.4 with sodium hydroxide, 1.0 ml of the amide local anesthetic dissolved in deionized water (or the phosphate buffer described) and 4 ml of $3.75 \times 10^{-5}M$ chloroprocaine hydrochloride dissolved in the phosphate buffer. The control reaction mixture was as described except that the 1.0 ml of amide anesthetic solution was replaced by 1.0 ml of phosphate buffer or deionized water. A sample prepared as described except that 4.0 ml of phosphate buffer replaced the chloroprocaine solution was used as a blank for the spectrophotometric measurements. In the studies which examined the possibility that the estimates of percent inhibition might be related to the concentration of serum in the reaction mixture (ie, to determine if the altered milieu in which the enzyme was studied yielded artifactual inhibition), the assay system was as above except that the volume of serum and buffer were changed to yield final serum concentrations in the reaction mixture ranging from 0.86 to 16.7%. Finally, a set of experiments was run using a reaction mixture of 3 ml of serum, 0.5 ml of $9 \times 10^{-5}M$ bupivacaine (or 0.5 ml of deionized water in the control studies), and 0.5 ml of $1.5 \times 10^{-3}M$ chloroprocaine. This markedly increased chloroprocaine concentration was used to improve the accuracy of the measurement of the rate of hydrolysis of substrate at nearly physiological enzyme concentration.

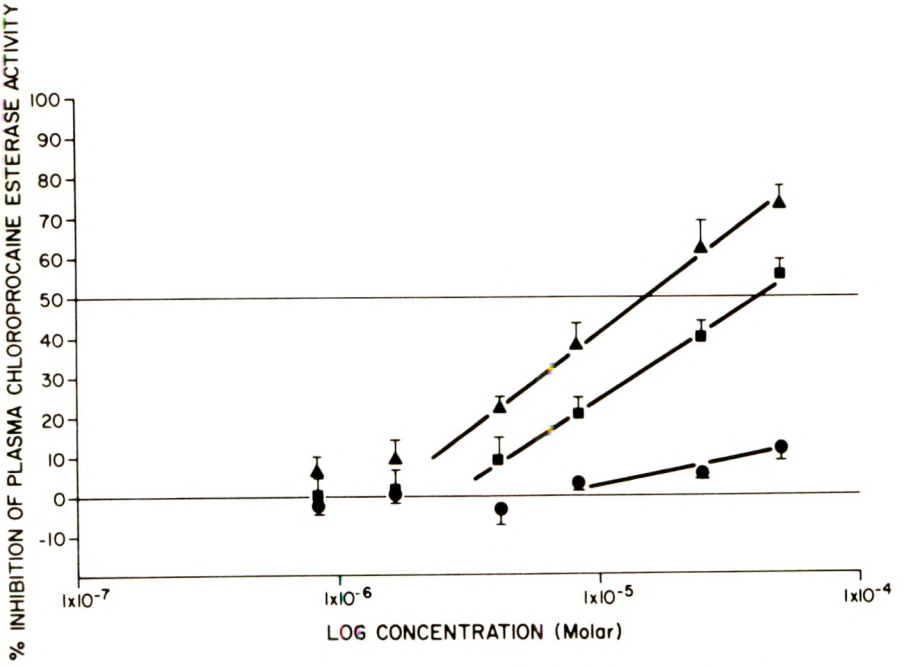


FIG 1. Effect of drug concentration on percentage of inhibition of human serum chloroprocaine esterase activity for bupivacaine (▲), etidocaine (■), and mepivacaine (●). The data are presented as the population mean ± 1 SD.

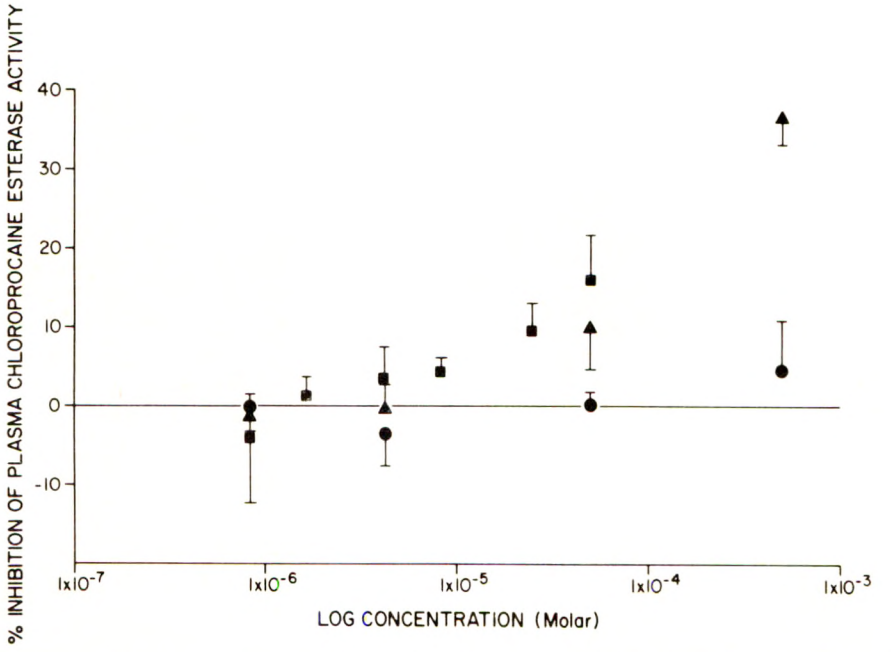


FIG 2. Effect of drug concentration upon percent inhibition of human serum chloroprocaine esterase activity for lidocaine (■), monoethyl glycine xylidide (▲), and glycine xylidide (●). The data are presented as the population mean ± 1 SD.

RESULTS

The effect of the concentration of the amide local anesthetics upon the rate of hydrolysis of chloroprocaine by human serum is shown in fig 1 and 2. It can be seen that bupivacaine and etidocaine cause 38 and 21% inhibition at $8.3 \times 10^{-6}M$ (about 2.4 μg/ml) while a concentration of $4.2 \times 10^{-6}M$ produced 22 and 9% inhibition, respectively (fig 1). The difference in degree of inhibition produced by these two drugs is statistically significant ($p<0.001$) at these concentrations. Mepivacaine (fig 1), lidocaine, monoethylglycine xylidide, and glycine xylidide (fig 2) caused no significant inhibition at concentrations below $2 \times 10^{-5}M$.

Some characteristics of the plasma cholinesterase mediated hydrolysis of chloroprocaine are summarized in fig 3 to 5. Specifically, the control data in fig 3 show that the rate of chloroprocaine hydrolysis appears to be a simple linear function of time at least for all concentrations of chloroprocaine between 0.4 and $1.7 \times 10^{-4}M$ (ie, the reaction proceeds at a zero-order rate, as shown in the control curve in fig 3; this rate is 1.87 nm hydrolyzed per second per millilitre of reaction mixture). Linear decline in substrate concentration as a function of time over a broad range of substrate concentration is a characteristic of an enzyme catalyzing a process at or near a maximal rate (ie, very near the enzyme's V_{max}). Thus,

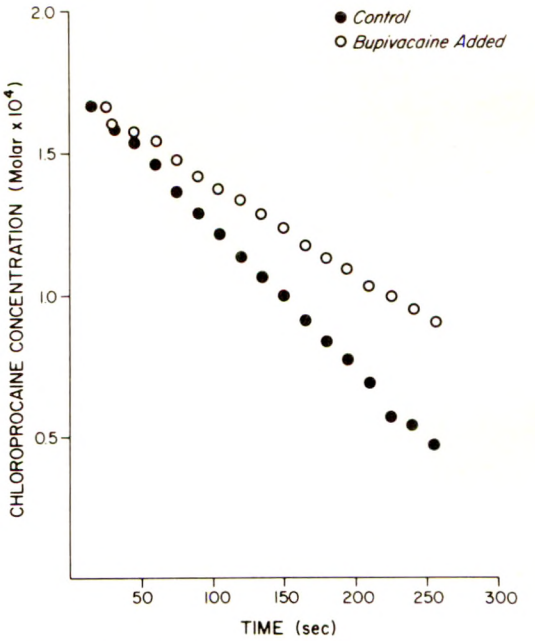


FIG 3. Rate of change of chloroprocaine concentration in the presence and absence of bupivacaine when the final concentration of serum in the reaction mixture is near physiological (ie, the reaction mixture is 75% serum). The concentration of bupivacaine in this experiment was $1.1 \times 10^{-5}M$.

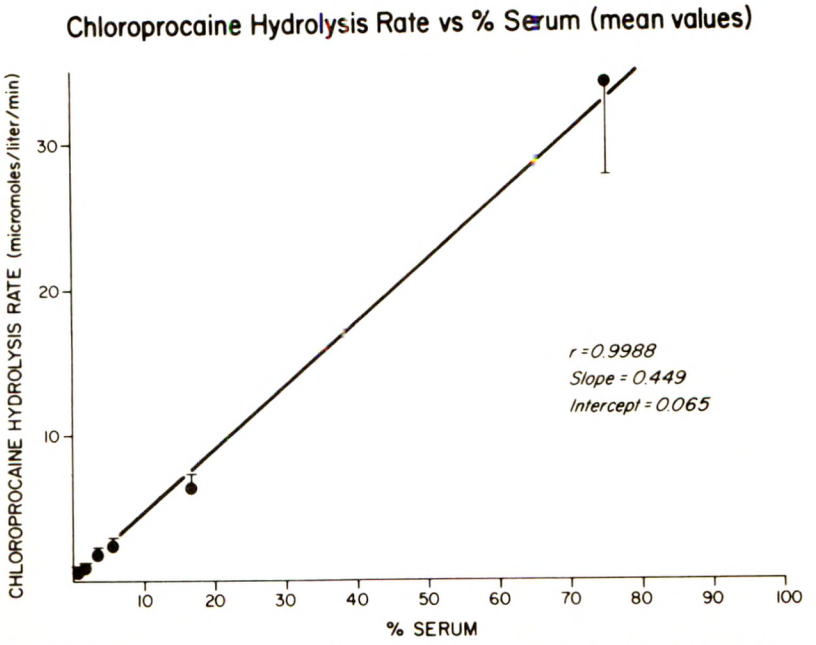


FIG 4. The relationship of enzyme concentration (percentage of the reaction mixture composed of serum) and the rate of hydrolysis of chloroprocaine. The data are presented as the population mean ± 1 SD.

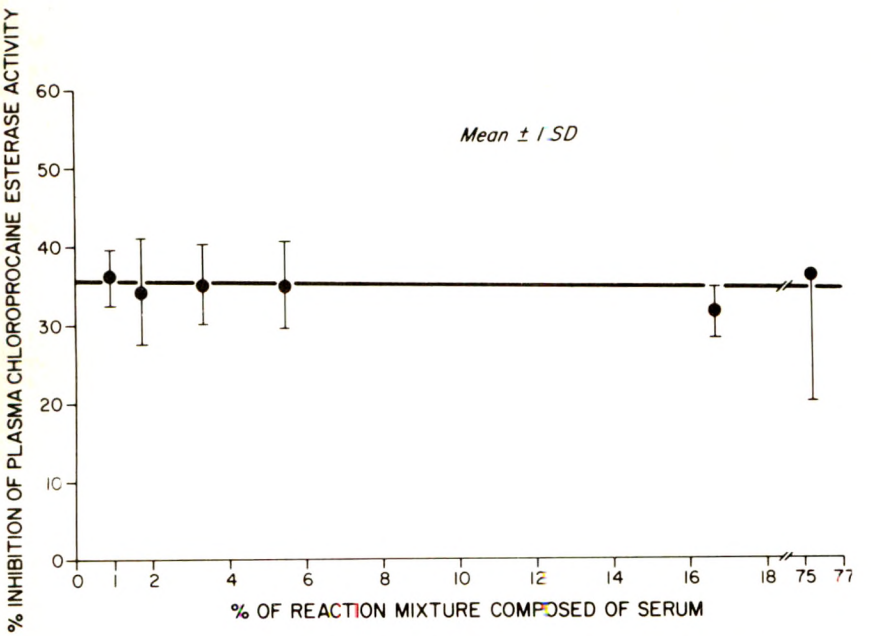


FIG 5. The relationship of enzyme concentration (percentage of the reaction mixture composed of serum) and the observed percentage inhibition of chloroprocaine hydrolysis. Note that the enzyme concentration, as well as the markedly altered milieu in which the assay was conducted (ie, serum concentrations varying from 0.86 to 75%), did not influence the inhibition process.

1.87 nm/sec/ml of reaction mixture is a reasonable estimate of V_{max}.

The data in fig 4 strongly suggest that the absolute rate of chloroprocaine hydrolysis is a linear function of enzyme concentration. Furthermore, the data in fig 5 establish that the magnitude of the observed inhibition is not significantly influenced by enzyme concentration. These latter points are significant because the "plasma cholinesterase activity" of human serum probably

resides in a group of proteins which may represent a monomer and three different aggregates of this monomer.[5] Since dilution might be expected to influence the relative concentration of the various aggregates, it was necessary to show that the rate of hydrolysis of substrate (see fig 4) and the inhibition of ester hydrolysis (see fig 5) were not influenced by changes in the milieu which are required to make accurate estimates of the hydrolysis rate.

DISCUSSION

Synergistic toxicity following the simultaneous administration of local anesthetics has been documented in laboratory animals[3] but the data in man[1] are not conclusive. One possible mechanism for an increase in toxicity is the inhibition of the metabolism of an ester anesthetic by an amide anesthetic (or by another ester agent which has a higher affinity for the enzyme and/or a lower susceptibility to hydrolysis) when the two are administered at the same time. The observations previously described demonstrate such inhibition and suggest the possibility of a significant drug-drug interaction under clinical conditions when bupivacaine or etidocaine are administered with chloroprocaine.

The inhibition of one metabolic pathway need not give rise to a clinically significant drug-drug interaction. Other criteria must be fulfilled. For example, the inhibited metabolic process must represent a large component of the overall disposition of the drug. The data in fig 3 and 4 as well as the studies of Foldes et al[4] strongly suggest that plasma is a very important site of chloroprocaine metabolism. Specifically, it has been reported that 1 ml of human plasma can hydrolyze 3.66 μmoles of chloroprocaine in 30 minutes[4] and that the substrate concentration which yields a half-maximal hydrolytic rate (ie, the apparent K_m) is about $2 \times 10^{-6} M$.[6] These data suggest that 3 L of serum could hydrolyze 366 μmoles (99 mg) of chloroprocaine per minute if substrate concentration were maintained at a sufficiently high level (3-4 $\times$ K_m or 0.81-1.08 μg/ml). The difficulties in measuring plasma levels of chloroprocaine following its epidural or IV administration have only recently been overcome, by Raj et al.[7] These investigators have reported mean peak arterial plasma levels of chloroprocaine as high as 8 μg/ml. Even at a plasma concentration of 8 μg/ml, the patient's plasma would be expected to be a far more important site of chloroprocaine metabolism than the liver because of hepatic perfusion limitations. That is, assuming a blood concentration of 8 μg/ml, a hepatic blood-flow rate of 1500 ml/min, and a hepatic extraction ratio of unity, the liver could only metabolize 12 mg/min. At this same blood concentration, the plasma could be expected to hydrolyze approximately 100 mg/min. Hence, it seems unlikely that the liver approaches the plasma in importance as a metabolic organ for chloroprocaine. Furthermore, the serum and hepatic enzymes seem to share many characteristics, which may include sensitivity to inhibitors.[8]

To evaluate the possible clinical importance of this drug interaction, it is necessary to estimate the toxicological importance of a 10 to 50% decrease in the rate of chloroprocaine metabolism. The results from a study in which chloroprocaine was infused IV suggest that chloroprocaine (approximately 1400 mg over 20 min) causes dose-related increases in pulse rate, blood pressure, and respiratory rate as well as ECG changes.[9] These responses were sufficiently severe that the infusion was terminated before the end of the study in 2 of 12 subjects. Thus, a moderate increase in dose or its functional equivalent, ie, inhibition of metabolism, may have significant toxicological consequences.

Moore et al have suggested 1000 mg of chloroprocaine, ie, a dose which is frequently given for epidural anesthesia when the drug is used alone, could be combined with agents such as mepivacaine and lidocaine without added toxicity.[1] The data presented in fig 1 and 2 suggest that only a very moderate metabolic interaction between chloroprocaine and either of these drugs would be expected and, therefore, that synergistic toxicity via the mechanism discussed in this text is unlikely. However, epidural administration of a dose of chloroprocaine of that magnitude combined with 100 to 400 mg of bupivacaine or 225 to 450 mg of etidocaine might be expected to increase the probability of toxic effects. This conclusion is justified because it is well documented that epidural doses of bupivacaine as low as 150 mg (20 ml of 0.75% containing 1:200,000 epinephrine) yield *mean* peak venous plasma concentrations of 1.0 μg/ml.[10] Thus, following even this modest dose, it would be expected that, on the average, the rate of chloroprocaine metabolism would be signifi-

cantly inhibited. Similarly, Thomas et al[11] found that the mean venous plasma concentration of bupivacaine was 1.0 μg/ml at time of delivery in 31 obstetric patients (mean dose was 107 mg). The highest venous plasma concentration reported by these workers was 2.2 μg/ml, which would be expected to cause a 35% inhibition of the rate of chloroprocaine hydrolysis. Larger epidural (225 mg) or intercostal (400 mg) doses of bupivacaine yield mean peak venous plasma concentrations of 1.0 and 2.5 μg/ml, respectively, and the simultaneously determined arterial plasma levels were 1.45 and 2.9 μg/ml, respectively.[10] Clearly these concentrations of bupivacaine should cause a significant level of inhibition in vivo. Finally, it should be noted that other investigators have suggested much higher venous levels of bupivacaine following such doses.[12] These data strongly suggest the possibility of a significant interaction between bupivacaine and chloroprocaine when high doses of bupivacaine are used.

On a milligram-of-drug basis, etidocaine yields blood and plasma levels which are somewhat lower than those seen following bupivacaine administration. However, since etidocaine is a somewhat less potent local anesthetic than bupivacaine and, hence, larger doses are often used, it too may cause significant inhibition of chloroprocaine hydrolysis in vivo. For example, Lund et al have reported peak venous *blood* concentrations of 3.2 μg/ml following a 450-mg epidural dose of etidocaine.[12] Since the red-blood-cell/plasma equilibrium of etidocaine strongly favors the partitioning of this drug into the plasma phase of whole blood, a blood level of 3.2 μg/ml may represent a plasma concentration (the actual site of ester hydrolysis) of 4.5 μg/ml or more.[13] Thus, the drug interactions which were the subject of the present study may be toxicologically significant. Finally, all these estimates of percent inhibition for a given bupivacaine or etidocaine plasma concentration may be underestimates of the inhibition which occurs in vivo because metabolites of these drugs might also contribute to in vivo inhibition.

It should be noted that preliminary results[14] suggest that procaine hydrolysis by human plasma is inhibited even more strongly than is that of chloroprocaine. Unfortunately, these studies have not yet been extended to such important plasma cholinesterase substrates as succinylcholine.

In conclusion, the available data suggest that care should be taken in the combination of chloroprocaine with etidocaine and bupivacaine in clinical anesthesiology. Furthermore, it may not be prudent to combine chloroprocaine with new local anesthetic agents until appropriate in vitro interaction studies have been performed.

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Cardiovascular Effects of Metocurine During Enflurane Anesthesia in Man

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The cardiovascular effects of 3 doses of metocurine (dimethyltubocurarine) were determined in 60 A.S.A. Class 1 or 2 patients anesthetized with low or high concentrations of enflurane-N_2O. In 30 patients, mean arterial blood pressure was 60 to 75 torr during anesthesia with inspired concentrations of 2.5 to 3.5% enflurane and 50% N_2O-O_2. Ten of these patients (Group I) were to receive metocurine 0.03 mg/kg, another 10 (Group II) metocurine 0.06 mg/kg, and a final 10 (Group III) metocurine 0.12 mg/kg. Thirty of the patients had mean arterial blood pressure between 75 and 90 torr with 1.5 to 2.5% enflurane and 50% N_2O-O_2. Ten of these patients (Group IV) were to receive metocurine 0.03 mg/kg, another 10 (Group V) metocurine 0.06 mg/kg, and a final 10 (Group VI) metocurine 0.12 mg/kg. Stroke volume, heart rate, cardiac output, mean arterial and central venous blood pressures, and peripheral arterial resistance were determined before and at 3-minute intervals up to 15 minutes after administration of metocurine.

Before administration of metocurine, Groups IV, V, and VI had significantly higher stroke volumes, cardiac outputs, mean arterial pressures, and lower peripheral vascular resistances than Groups I, II, and III but similar heart rates and central venous pressures. Groups I to IV sustained no significant change in any variable at any time after administration of metocurine. Patients in Groups V and VI experienced transient reductions in mean arterial pressure and peripheral arterial resistance 3 minutes after metocurine but sustained no significant change in any of the other cardiovascular variables measured. These data demonstrate that both low and high doses of metocurine produce minimal effects on cardiovascular dynamics during light or deep enflurane-N_2O anesthesia in man.

Key Words—NEUROMUSCULAR RELAXANTS, metocurine. ANESTHETICS, volatile, enflurane.

RECENT studies have demonstrated that metocurine (dimethyltubocurarine) produces little change in cardiovascular dynamics in patients anesthetized with N_2O-thiopental[1] or halothane-N_2O.[2,3] The effects of metocurine on cardiovascular dynamics during enflurane anesthesia have not been investigated. In this study we measured the effects of 3 doses of metocurine on cardiovascular dynamics during enflurane-N_2O-O_2 anesthesia in 60 adult A.S.A. Class 1 or 2 patients about to undergo a variety of intracranial or major abdominal operations.

METHODS

Written informed consent was obtained from each of the patients at the time of the preoperative visit. All patients were scheduled to undergo elective operations and were without cardiovascular disease. Premedications included pentobarbital (50 to 100 mg) and atropine (0.4 to 0.5 mg) IM 90 minutes before the scheduled operation. Prior to anesthesia, an IV infusion was started in an upper extremity, a central venous pressure catheter was placed percutaneously into the right atrium from the antecubital fossa or neck, and a radial or brachial artery catheter was inserted percutaneously and threaded 30 to 72 cm into the central aorta. The aortic-pressure catheter was attached via an arterial-pressure transducer to a central digital computer substation in the operating room. After appropriate calibration as previously described,[4] Warner's method of analyzing the central aortic pulse-pressure curve was used to determine cardiac output, stroke volume, arterial blood pressure, and peripheral arterial resistance.[4]

Following 5 minutes of breathing 100%

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O_2, all patients were anesthetized with thiopental 4 mg/kg, paralyzed with succinylcholine 1.5 mg/kg, and intubated tracheally. Respirations were mechanically controlled at volumes and rates necessary to keep $Paco_2$ between 30 and 35 torr as measured in arterial blood every 15 minutes. Thirty of the patients had anesthesia maintained with anesthetic-machine inflow concentrations of enflurane of 2.5 to 3.5% (issuing from a calibrated Ohio enflurane vaporizer) and 50% N_2O in O_2 so that mean arterial blood pressure was kept between 60 and 75 torr. Ten of these patients (Group I) were to receive metocurine 0.03 mg/kg, another 10 (Group II) metocurine 0.06 mg/kg, and a final 10 (Group III) metocurine 0.12 mg/kg. The remaining 30 patients had anesthesia maintained with inflow concentrations of enflurane of 1.5 to 2.5% and 50% N_2O in O_2 so that mean arterial blood pressure was kept between 75 and 90 torr. Ten of these patients (Group IV) were to receive metocurine 0.03 mg/kg, another 10 (Group V) metocurine 0.06 mg/kg, and a final 10 (Group VI) metocurine 0.12 mg/kg.

Measurements of cardiovascular dynamics were made a minimum of 30 minutes following any change in enflurane concentration either before operation or 30 to 40 minutes following initiation of surgery during periods of minimal and consistent surgical stimulation. Data were obtained before and at 3-minute intervals up to 15 minutes after administration of metocurine. No other supplemental anesthetic was employed prior to or during periods of data collection.

Neuromuscular blockade was measured in 6 patients each of Groups I, II, IV, and V and in all patients in Groups III and VI. Evaluation of blockade was made immediately before and 10 minutes after administration of metocurine. Force of thumb adduction in response to stimulation of the ulnar nerve at the wrist was measured with a Grass FT-10 force-displacement transducer and recorded on a Grass polygraph.

RESULTS

Patients were of a similar age and weight in all groups. Patients in Groups I, II, and III received an average inflow concentration of enflurane of 3.0 ± 0.3% and those in Groups IV, V, and VI, 2.1 ± 0.4%. Groups IV, V, and VI had significantly higher stroke volumes, cardiac outputs, and mean arterial pressures and lower peripheral vascular resistances than Groups I, II, and III but similar heart rates and central venous pressures (table). Changes in cardiovascular dynamics following metocurine were similar when obtained before or during operation; therefore, data obtained before and during operation were combined. Groups I to IV sustained no significant change in any variable at any time after administration of metocurine. Patients in Groups V and VI experienced transient reductions in mean arterial blood pressure and peripheral arterial resistance 3 minutes after metocurine 0.06 and 0.12 mg/kg but sustained no significant change in any of the other cardiovascular variables measured.

Metocurine depressed twitch an average of 53 ± 8, 86 ± 6, 31 ± 9, and 71 ± 8% 10 minutes after administration in Groups I, II, IV, and V, respectively. Metocurine completely abolished twitch in Groups III and VI.

DISCUSSION

Intravenous administration of d-tubocurarine, particularly large doses, is often followed by hypotension during general anesthesia.[2] Pancuronium, on the other hand, frequently produces[5] or augments[6] tachycardia and/or hypertension when given during induction or maintenance of states of general anesthesia. Each of the above changes in cardiovascular dynamics may be detrimental in certain patients. A number of recent studies[1-3] have demonstrated that metocurine produces little change in cardiovascular dynamics in patients anesthetized with N_2O-narcotic-thiopental or halothane-N_2O. The results of this investigation demonstrate that modest doses of metocurine and doses adequate to completely abolish thumb-adduction twitch have little influence on cardiovascular dynamics during deep levels of enflurane-N_2O anesthesia and produce only small and transient decreases in arterial blood pressure and peripheral arterial resistance at lighter levels of enflurane-N_2O anesthesia.

The benignity of metocurine on cardiovascular dynamics during general anesthesia is probably related to the apparent lack of effect of metocurine on cardiac vagal fibers (in contrast to gallamine and pancuronium) and its greater neuromuscular blocking potency and lesser autonomic inhibiting and histamine-releasing potency (in contrast to d-tubocurarine).[1] The difference in dosage necessary to produce neuromuscular versus autonomic inhibition or histamine release

TABLE

Cardiovascular Effects of Metocurine During Enflurane-N_2O Anesthesia
(Mean ± SD)

	Anesthetic depth	Group	Control	Minutes after metocurine 3	6	9	12	15
Heart rate (beats/min)	Deep	I	72 ± 6	79 ± 8	78 ± 7	72 ± 7	71 ± 7	73 ± 8
		II	72 ± 6	81 ± 9	73 ± 6	73 ± 6	72 ± 7	70 ± 9
		III	73 ± 6	81 ± 8	77 ± 8	77 ± 8	73 ± 7	71 ± 8
		IV	75 ± 7	79 ± 7	77 ± 7	77 ± 8	76 ± 8	77 ± 8
	Light	V	74 ± 8	81 ± 9	80 ± 9	78 ± 7	73 ± 5	72 ± 8
		VI	75 ± 8	82 ± 10	81 ± 10	77 ± 8	75 ± 7	72 ± 8
Stroke volume (beats/min)	Deep	I	36 ± 5*	34 ± 5*	34 ± 5*	34 ± 6*	35 ± 6*	35 ± 5*
		II	35 ± 6*	31 ± 5*	32 ± 5*	34 ± 5*	35 ± 5*	35 ± 5*
		III	36 ± 6*	31 ± 6*	31 ± 5*	33 ± 6*	36 ± 5*	36 ± 6*
		IV	44 ± 5	42 ± 5	43 ± 6	43 ± 5	44 ± 5	44 ± 5
	Light	V	45 ± 5	44 ± 6	42 ± 6	42 ± 5	44 ± 5	44 ± 5
		VI	45 ± 5	42 ± 5	41 ± 5	43 ± 5	44 ± 5	45 ± 5
Cardiac output (l/min)	Deep	I	2.6 ± 0.4*	2.7 ± 0.4*	2.7 ± 0.4*	2.5 ± 0.5*	2.5 ± 0.5*	2.6 ± 0.5*
		II	2.5 ± 0.4*	2.5 ± 0.4*	2.4 ± 0.4*	2.5 ± 0.4*	2.5 ± 0.4*	2.5 ± 0.4*
		III	2.5 ± 0.4*	2.4 ± 0.4*	2.3 ± 0.4*	2.5 ± 0.4*	2.5 ± 0.4*	2.5 ± 0.4*
		IV	3.3 ± 0.5	3.3 ± 0.5	3.3 ± 0.4	3.3 ± 0.4	3.3 ± 0.4	3.4 ± 0.4
	Light	V	3.3 ± 0.5	3.5 ± 0.5	3.4 ± 0.4	3.4 ± 0.5	3.2 ± 0.4	3.2 ± 0.4
		VI	3.4 ± 0.5	3.6 ± 0.5	3.5 ± 0.4	3.4 ± 0.5	3.3 ± 0.4	3.3 ± 0.4
Mean arterial blood pressure (torr)	Deep	I	69 ± 7*	64 ± 6*	65 ± 7*	67 ± 7*	67 ± 7*	67 ± 7*
		II	70 ± 8*	62 ± 8*	62 ± 8*	66 ± 8*	68 ± 9*	70 ± 8*
		III	71 ± 8*	64 ± 8*	64 ± 8*	65 ± 8*	68 ± 9*	69 ± 8*
		IV	81 ± 7	74 ± 7	78 ± 9	79 ± 8	82 ± 7	82 ± 7
	Light	V	82 ± 6	72 ± 7†	76 ± 8	79 ± 8	82 ± 7	82 ± 7
		VI	82 ± 7	71 ± 7†	72 ± 7†	78 ± 7	81 ± 7	82 ± 7
Central venous pressure (torr)	Deep	I	9 ± 2	8 ± 3	8 ± 3	8 ± 3	9 ± 3	9 ± 2
		II	9 ± 2	7 ± 3	8 ± 3	8 ± 3	9 ± 3	8 ± 3
		III	9 ± 2	7 ± 3	8 ± 3	8 ± 3	9 ± 3	9 ± 2
		IV	9 ± 3	7 ± 2	7 ± 2	7 ± 2	9 ± 2	8 ± 3
	Light	V	9 ± 3	6 ± 2	7 ± 2	8 ± 3	9 ± 2	8 ± 2
		VI	9 ± 3	8 ± 2	8 ± 2	8 ± 3	9 ± 2	9 ± 2
Peripheral arterial resistance (PRU)‡	Deep	I	25.7 ± 0.6*	24.1 ± 0.7*	24.0 ± 0.7*	26.5 ± 0.7*	26.4 ± 0.7*	25.4 ± 0.8*
		II	26.7 ± 0.7*	25.3 ± 0.4*	25.4 ± 0.7*	26.0 ± 0.6*	26.3 ± 0.8*	27.6 ± 0.7*
		III	26.1 ± 0.7*	25.4 ± 0.4*	25.6 ± 0.7*	25.8 ± 0.7*	26.2 ± 0.8*	26.6 ± 0.8*
		IV	23.4 ± 0.6	22.4 ± 0.6	23.6 ± 0.8	24.5 ± 0.7	24.2 ± 0.8	24.1 ± 0.7
	Light	V	23.9 ± 0.8	22.1 ± 0.6†	22.3 ± 0.6	23.6 ± 0.7	25.0 ± 0.7	24.3 ± 0.7
		VI	24.1 ± 0.7	22.1 ± 0.5†	22.3 ± 0.7	23.3 ± 0.7	24.2 ± 0.8	24.8 ± 0.7

*$p<0.05$, Student's unpaired t-test when compared to Groups IV, V, or VI at the same time

†$p<0.05$, Student's paired t-test when compared to control values

‡Peripheral resistance units

Anesth Analg 57:540-543, 1978

has been termed "the autonomic margin of safety" by Savarese et al[1] and has been shown to be greater for metocurine than for d-tubocurarine in patients anesthetized with N_2O-morphine-thiopental anesthesia. A comparative analysis of the autonomic margin of safety of d-tubocurarine and metocurine has yet to be accomplished in patients anesthetized with enflurane-N_2O. However, comparison of cardiovascular changes observed following metocurine during enflurane-N_2O anesthesia in this study with doses of d-tubocurarine adequate to reduce thumb-adduction twitch height 90 to 100% during enflurane-N_2O anesthesia (Stanley TH, unpublished data), suggest that metocurine has a greater autonomic margin of safety than d-tubocurarine during this technic.

Metocurine 0.06 and 0.12 mg/kg produced small, transient decreases in peripheral arterial resistance and mean arterial blood pressure in Groups V and VI patients. Similar changes in both variables have been found after metocurine in patients anesthetized with halothane-N_2O and N_2O-morphine.[1-3] Causes of these changes could include the preservative (0.5% phenol) in metocurine, histamine release, or a direct effect of metocurine on the myocardium and/or the peripheral vasculature. Unfortunately, little information exists regarding metocurine's effects on myocardial mechanics and vascular smooth muscle. Furthermore, histamine blood levels could not be measured in this study, nor could the blood-pressure and peripheral-arterial-resistance responses to phenol be determined.

Savarese et al[1] found that 0.28 mg/kg of metocurine was required to reduce thumb-adduction twitch 95% in patients anesthetized with N_2O-morphine-thiopental. Stoelting[2] showed that 0.2 mg/kg of metocurine was necessary to abolish twitch in patients anesthetized with halothane-N_2O. The doses of metocurine employed in this investigation were chosen to produce various degrees of neuromuscular blockade during light and deep levels of enflurane-N_2O anesthesia. Our results demonstrate that metocurine 0.12 mg/kg completely abolishes thumb-adduction twitch irrespective of the concentration of enflurane employed, and metocurine 0.06 mg/kg produces 86 and 71% average decreases of twitch in deeply and lightly enflurane-N_2O anesthetized patients, respectively. These data when combined with those of Savarese and Stoelting indicate that metocurine is a significantly more potent neuromuscular blocker during enflurane-N_2O than during halothane-N_2O or N_2O-narcotic anesthesia. They also suggest that metocurine neuromuscular blockade is potentiated by anesthetic depth during enflurane anesthesia. Similar results have been obtained when comparisons of the potency of d-tubocurarine have been made during enflurane, halothane, and N_2O-narcotic anesthesia[7] and when the potency of d-tubocurarine has been compared during different depths of enflurane anesthesia.[8]

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Comparison of Spread of Epidural Anesthesia in Pregnant and Nonpregnant Women

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Using a standardized epidural anesthetic technic, we compared levels of sensory anesthesia in patients undergoing cesarean section and in nonpregnant women undergoing elective surgery. When equal volumes of local anesthetic solutions were injected (either 15 ml or 20 ml of 0.75% bupivacaine without epinephrine), there was no statistically significant difference in sensory levels in pregnant and nonpregnant patients.

Key Words — ANESTHETIC TECHNICS, peridural. ANESTHESIA, obstetric.

That decreased volumes of local anesthetic solutions are required for epidural anesthesia in the term pregnant female is widely accepted. Our clinical impression was that the magnitude of this effect was not as great as has been suggested.[1] We therefore prospectively gathered data to reassess the influence of pregnancy on the spread of anesthesia after epidural injection of local anesthetics.

MATERIALS AND METHODS

In our institution the technic of lumbar epidural anesthesia has been standardized: an epidural needle is introduced in the 3rd lumbar interspace, the epidural space identified by the loss of resistance technic, and, with the bevel pointed cephalad, a multiple of 5 ml of local anesthetic is injected at a rate of 1 ml/sec. It has been the practice of one of us (EMG) to use 15 ml of 0.75% bupivacaine for cesarean section (CS), while one of us (AZ) uses 20 ml of 0.75% bupivacaine. Our control group consisted of nonpregnant female patients under the age of 40 years undergoing elective surgery who received either 15 ml or 20 ml of 0.75% bupivacaine in the epidural space as described above. In none of these cases was epinephrine added to the bupivacaine.

In all cases the local anesthetic was administered through the needle with the patient in lateral position on a horizontal operating table. A catheter was then also threaded into the epidural space if indicated. Immediately upon completion of the injection, the patient was placed in the supine position and the spread of anesthesia assessed by observing the highest level of loss of sharpness to pinprick 8 and 15 minutes after the injection. In all the pregnant patients, either left lateral tilt of the table or left uterine displacement was employed to avoid vena caval compression.

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TABLE

Data for Cesarean Section Patients and Control, Nonpregnant Patients

Group	Age in yrs (mean ± SD)	Height in cm (mean ± SD)	Weight in kg (mean ± SD)	Upper level* (mean ± SD)
15-ml** control (♀<40) $n = 32$	29.2 ± 5.7	161.5 ± 6.9	69.5 ± 15.0	5.7 ± 1.7
15 ml for CS $n = 60$	24.6 ± 5.7	158.0 ± 6.6	70.9 ± 12.2	5.5 ± 1.2
20-ml control (♀<40) $n = 29$	28.4 ± 5.6	160.2 ± 6.9	65.6 ± 13.8	4.7 ± 1.7
20 ml for CS $n = 29$	24.8 ± 7.3	158.5 ± 5.4	69.6 ± 11.9	4.2 ± 1.5

*Most cephalad thoracic dermatome made anesthetic to pinprick
**Volume of bupivacaine (0.75%) injected into the epidural space

RESULTS

Regression lines were calculated to evaluate the possible relationships between level of anesthesia and the age or height of patients. None of these lines achieved statistical significance, and so each of these parameters was treated simply as a normal distribution. The table shows the mean age, height, weight, and upper level of anesthesia in each of the 4 groups. In all cases, perineal anesthesia was obtained. Student's *t*-test for unpaired data showed that at the 5% level of significance, the CS patients were both younger and shorter than the control patients, but that there was no significant difference in weight. When equal volumes of local anesthetic solution were injected, there was no significant difference between the CS group and the control group in the extent of the resulting anesthesia. Spread of local anesthetic solution was, however, significantly less following 15 ml of local anesthetic solution than it was following injection of 20 ml.

DISCUSSION

The association between term pregnancy and increased spread of local anesthetic during epidural anesthesia is widely accepted. We were therefore surprised when we found no statistically significant difference between our CS patients and our nonpregnant control patients in the extent to which the anesthetic spread after injection of either 15 ml or 20 ml. It is perhaps unfortunate that our control groups were not identically matched to the CS groups. This is not surprising, since the average patient undergoing CS tends to be young, of short stature, and carrying about 9 kg of products of conception. The control groups were older and taller than the CS groups, but not significantly different in weight. Although regression lines showed no significant correlation between level of anesthesia and either age or height, classical teaching would have us believe that the CS patient would have decreased spread of anesthesia because of her younger age while her shortness in height would lead to an increased spread. We do not feel that the magnitude of the conflicting effects of these 2 variables is enough to hide a true difference between our CS patients and our controls.

The accepted mechanism of the putative increased spread of epidural local anesthetic solutions is that the gravid uterus presses backward onto the inferior vena cava, thereby occluding it. Venous return from the lower extremities and pelvis occurs via the vertebral venous plexus to the azygos vein and thence to the right heart. Because the epidural veins become distended at term, the volume of epidural space per spinal segment is therefore theoretically decreased. This mechanism has been shown to operate in a dog model.[2] The importance of inferior vena caval compression in the supine pregnant patient was not recognized until 1968 in the anesthetic literature,[3] and therefore was almost certainly present but unrecognized in Bromage's original series, reported in 1962.[1] It is possible that the precautions that we used to prevent occult caval compression in our pregnant horizontal patients (left lateral table tilt or left uterine displacement) were so effective at relieving compression that the epidural veins were essentially returned to their nonpregnant state.

In comparing our results with those reported by Bromage,[1] we find that he used varying volumes of local anesthetic when comparing his 40 pregnant women at term with his control group (which included both males and elderly patients). It has been suggested elsewhere that the dose required per segment varies with the volume injected;[4] and our results show that the increase from 15 to 20 ml of injectate resulted in, on an average, the blockade of only 1 additional segment, confirming this observation. The use of 2 relatively different populations in the study makes Bromage's work difficult to evaluate. Other workers have agreed with Bromage's conclusions[5] until the appearance of a control group changed their views.[6]

In conclusion, we agree with the results of Kalas et al[6] in that we find no evidence of increased spread of local anesthetic in the epidural space of the pregnant female at term. We mention the possible role of relief of occult vena caval compression but find more impressive the lack of a good controlled study in the literature documenting increased spread of anesthesia in the pregnant female at term.

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DIAZEPAM DOSE REQUIREMENTS

In 19 patients diazepam was administered IV in a dose just adequate to allow endoscopic intubation. A 22-fold variation was observed in the required dose of diazepam (median dose, 20 mg; range, 5 to 110 mg). Analysis of plasma samples for diazepam and N-desmethyl-diazepam revealed that the clinical response did not relate to the rate or character of initial drug distribution. There was a high correlation ($r = 0.96$) between the dose and the plasma concentration 10 minutes after administration. Users of diazepam displayed tolerance to its pharmacologic effects, requiring a significantly larger ($p<0.05$) dose than nonusers (median doses, 35.0 mg and 14.5 mg respectively). Older patients required less than younger patients ($r = -0.54$, $p<0.05$). The variation between individuals in the dose of diazepam required as preparation for endoscopy cannot be explained by variation in drug disposition but instead reflects previous diazepam use, age, and probably differences in sensitivity at the site or sites of drug action. *(Giles HG, MacLeod SM, Wright JR, et al: Influence of age and previous use on diazepam dosage required for endoscopy. Can Med Assoc J 118:513-514, 1978)*

Epinephrine-Induced Arrhythmias During Enflurane Anesthesia in Man: A Nonlinear Dose-Response Relationship and Dose-Dependent Protection from Lidocaine

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Forty-eight patients undergoing transsphenoidal pituitary surgery under enflurane anesthesia received submucosal injections of 1:150,000 or 1:200,000 epinephrine in saline, 0.5% lidocaine, or 1.0% lidocaine. The threshold doses for ventricular irritability, defined as 3 or more premature ventricular contractions during or in the 3 to 5 minutes following injection, were 1.3 μg/kg with saline, 2.5 μg/kg with 0.5% lidocaine, and 4.9 μg/kg with 1.0% lidocaine. There was no consistent relationship between epinephrine dose and occurrence of ventricular irritability within or among groups. The data show a protective effect of lidocaine against epinephrine-induced ventricular irritability during enflurane anesthesia and suggest a qualitative as well as quantitative difference between enflurane and other volatile anesthetics in their interaction with epinephrine.

Key Words—HEART, arrhythmias. ANESTHETICS, local, lidocaine. SYMPATHETIC NERVOUS SYSTEM, epinephrine.

THE injection of epinephrine is widely used to achieve hemostasis during surgery. In a comparative study of anesthetic-epinephrine interactions in man, Johnston et al[1] found higher doses of epinephrine were required to produce ventricular irritability during enflurane or isoflurane anesthesia than during halothane anesthesia. They reported that the dose-response curve for epinephrine-induced arrhythmias with enflurane anesthesia was significantly flatter than that for halothane or isoflurane. This suggested possible qualitative as well as quantitative differences between enflurane and halothane or isoflurane in their effects on myocardial irritability. They also found that addition of 0.5% lidocaine to the epinephrine solution protected against arrhythmias during halothane anesthesia.

We undertook to confirm the interaction found by Johnston et al for enflurane and epinephrine. We also sought to determine whether lidocaine in the epinephrine solution provided the protection against arrhythmias during enflurane anesthesia that Johnston et al found during halothane anesthesia.

METHODS

This study was approved by the U.C.S.F. Committee on Human Research. We studied 48 patients (ASA Physical Status I or II) undergoing transsphenoidal pituitary sur-

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TABLE 1
Variables (± SEM) in Three Groups of Patients Receiving Different Concentrations of Lidocaine

Epinephrine with	*n*	Age (yrs)	Weight (kg)	$Paco_2$ (torr)	Maximum pulse rate	Maximum systolic pressure	Arrhythmic threshold dose (μg/kg)
Saline	16	32 ± 2.7	69 ± 4.4	35 ± 1.0	113 ± 6.0	145 ± 9.6	1.3
0.5% Lidocaine	16	43 ± 4.0*	71 ± 3.7	36 ± 0.7	106 ± 5.0	132 ± 8.3	2.5
1.0% Lidocaine	16	30 ± 2.3	70 ± 4.0	36 ± 0.7	114 ± 3.6	145 ± 7.0	4.9

*$p<0.05$

gery. Patients were randomly divided into 3 treatment groups (table 1). All were without evidence of significant cardiovascular disease. No premedication or IV inducing agent was given. All patients were anesthetized by mask with enflurane in O_2. After endotracheal intubation without the use of additional drugs, ventilation was controlled to produce an arterialized venous[2] Pco_2 of 30 to 40 torr, measured with a standard Severinghaus electrode. End-tidal enflurane (measured with a Beckman LB1 infrared analyzer) was ajdusted to and maintained at approximately 2.5% (1.5 MAC) during the subsequent 30 minutes required for positioning and preparation of the patient. A standard lead ECG with well-visualized P waves was recorded on a strip chart just before, during, and for 3 to 5 minutes after injection by the surgeon of the epinephrine-containing solution into the nasal and oral submucosa. All solutions were freshly prepared and contained epinephrine 1:150,000 or 1:200,000 in either normal saline, 0.5% lidocaine, or 1.0% lidocaine. The surgeon was not aware of the identity of the solution. The injections took from 2 to 6 minutes to complete, the volume injected being determined solely by surgical needs except that injection was halted if premature ventricular contractions (PVC's) occurred. Lidocaine was administered IV if PVC's became multifocal or caused a decrease in arterial blood pressure. Cuff blood pressure was recorded twice each minute during and immediately following injection.

We defined ventricular irritability as 3 or more PVC's occurring during or immediately following epinephrine injection. This is the definition used previously by Johnston et al. Presence or absence of ventricular irritability was plotted against dose of epinephrine administered.

To assess the significance of the relationship between occurrence of PVC's and lidocaine concentration of the injected solution, independence of lidocaine concentration and outcome was tested using the likelihood-ratio chi-square statistic.[3] Differences in other variables between groups were evaluated by Student's *t*-test.

RESULTS

Weight, $Paco_2$, and maximum pulse rate and blood pressure after epinephrine injection did not differ significantly among the 3 groups. Age was significantly greater in the patients receiving 0.5% lidocaine (table 1). The lowest dose of epinephrine at which ventricular irritability occurred in any patient (minimum threshold dose) increased from 1.3 to 2.5 to 4.9 μg/kg as the concentration of lidocaine in the epinephrine solution was increased from 0 to 0.5 to 1.0% (table 1). The likelihood-ratio chi-square statistic demonstrated that an increase in lidocaine concentration significantly ($p<0.05$) decreased the likelihood of occurrence of arrhythmias.

The figure illustrates individual results in the 3 groups. We did not calculate the dose of epinephrine-producing arrhythmias in 50% of patients (ED_{50}) because some patients received much greater doses of epinephrine than the minimum arrhythmic threshold dose without exhibiting ventricular irritability. This results in a flat or even (in the saline group) an inverse dose-re-

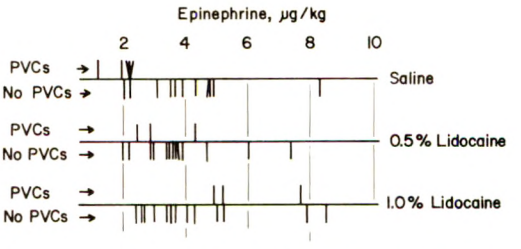


FIGURE. Individual results in 3 groups. Horizontal lines indicate dose of epinephrine injected. Each vertical deflection represents 1 patient; upward signifies a patient who had ventricular irritability, downward signifies one who did not.

sponse relationship. Most arrhythmias consisted of bigemini or multifocal PVC's and lasted for 1 to 2 minutes but caused no decrease in arterial blood pressure. One patient developed ventricular tachycardia followed by hypotension to 70 torr systolic, which reverted to sinus tachycardia and normal blood pressure after administration of IV lidocaine.

DISCUSSION

The lack of correlation of epinephrine dose with response during enflurane anesthesia seen by us was also found by Johnston et al[1] under similar clinical circumstances. In their study the dose of epinephrine required to induce PVC's in 50% of patients (ED_{50}) was 2.1 μg/kg for halothane, 6.7 μg/kg for isoflurane, and 10.9 μg/kg for enflurane. When halothane was used, no patient developed arrhythmias when less than 1.8 μg/kg (86% of the ED_{50}) was injected; when isoflurane was used, no patient developed arrhythmias when less than 5.4 μg/kg (81% of the ED_{50}) was injected; but when enflurane was used, one patient developed arrhythmias at 3.6 μg/kg and another at 5.1 μg/kg (33 and 47% of the ED_{50} respectively). Thus, the ratio between the lowest dose producing arrhythmias and the ED_{50} was smaller for enflurane than for halothane or isoflurane. Our findings agree with those of Johnston et al, adding further evidence for a possible qualitative as well as quantitative difference in the interaction of epinephrine with enflurane as compared to halothane and isoflurane.

In attempting to explain the wide variation in patient response to epinephrine under enflurane anesthesia, we rearranged the subjects into 2 groups, namely those having 3 or more PVC's and those not having 3 or more PVC's. The following comparisons can be made (table 2): age, weight, $Paco_2$, and dose of epinephrine did not differ significantly between the 2 groups, but maximum systolic blood pressure was greater in those patients who had ventricular irritability.

This greater increase in blood pressure in patients exhibiting ventricular irritability could play a role in the genesis of the arrhythmias. Several authors[4-6] have shown that less epinephrine is required to induce arrhythmias in dogs if the blood pressure is elevated. While the increase in arterial pressure that we observed may contribute to the arrhythmias, it also indicates, as do the PVC's themselves, a greater pharmacologic effect of epinephrine in these patients. This greater effect may be due to a greater uptake of epinephrine from the extremely vascular site of injection (or even intravascular injection) but it could also represent a more marked individual response to the same circulating dose of epinephrine. Blood epinephrine levels would further elucidate this relationship but these were not measured.

Our study and that of Johnston et al[1] show that arrhythmias can occur after doses of epinephrine in the range of 1 to 2 μg/kg during enflurane or halothane anesthesia. While ventricular irritability developed in patients anesthetized with halothane who received epinephrine doses only slightly greater than this minimum threshold dose, ventricular irritability did not appear in many enflurane-anesthetized patients who received doses of epinephrine far in excess of the minimum threshold dose.

Since epinephrine was rapidly administered into the oral and nasal submucosa, uptake was presumably quite rapid. Patients who developed arrhythmias always did so either during or within 2 minutes after injection. Patients receiving epinephrine injections into other anatomical areas might tolerate larger doses without ventricular irritability. Intravenously administered epinephrine would presumably cause arrhythmias at lower doses.

Our finding that lidocaine provides dose-

TABLE 2
Data (± SEM) for Patients Divided into Two New Groups by the Presence or Absence of Ventricular Irritability

	n	Epinephrine (μg/kg)	Maximum systolic pressure	Maximum pulse rate	End-tidal enflurane (%)	$Paco_2$ (torr)	Age (yrs)	Weight (kg)
PVC's	11	3.8 ± .5	172 ± 8.0*	118 ± 5.8	2.5 ± .07	34.8 ± 1.6	33.2 ± 2.7	70.4 ± 6.1
No PVC's	37	4.5 ± .5	139 ± 5.7*	108 ± 3.1	2.5 ± .04	36.2 ± .67	37.0 ± 3.0	70.9 ± 3.3

*$p<0.01$

dependent protection against epinephrine-induced ventricular irritability during enflurane anesthesia agrees with the results of Johnston et al[1] during halothane anesthesia. Katz[7] has found 2% lidocaine protective against epinephrine-induced arrhythmias in cats anesthetized with halopropane.

We did not measure blood lidocaine levels in our patients, some of whom received up to 500 mg of lidocaine over 4 or 5 minutes. We saw no signs of lidocaine toxicity, but this is certainly not surprising since general anesthesia would mask CNS toxicity and epinephrine would tend to counteract any cardiac toxicity. We also saw no evidence of the vasodilatory effect of lidocaine interfering with epinephrine-induced vasoconstriction but our only estimate of such an effect was blood loss estimated in the usual fashion. More careful investigation of this phenomenon might demonstrate that lidocaine does counteract the vasoconstrictive effect of injected epinephrine. We conclude that lidocaine should be added to all epinephrine solutions injected during inhalation anesthesia.

We as anesthetists cannot prevent rapid uptake of injected epinephrine or even intravascular injection, but we can influence the solution injected and the sensitivity of the patient to the arrhythmogenic effect. The available data suggest that if epinephrine is to be injected during inhalation anesthesia the patient will be less likely to develop ventricular irritability if enflurane rather than halothane is the anesthetic and if the injected solution contains lidocaine.

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DOPAMINE EFFECTS DURING PREGNANCY

Maternal and fetal cardiovascular and metabolic effects of dopamine were studied in awake pregnant ewes near term. Preparatory surgery under halothane anesthesia was done on 2 consecutive days, at least 48 hours prior to the study period. Dopamine was administered at randomly selected rates of 1, 3, 5, 10, 20, 30, or 40 μg/kg/min. Doses less than 10 μg/kg/min produced no significant change in maternal arterial blood pressure, cardiac output, or renal or uterine blood flow. Higher doses increased maternal cardiac output and blood pressure, did not change renal blood flow, but decreased uterine blood flow. Dopamine consistently caused mild maternal and fetal respiratory acidosis. *(Callender K, Levinson G, Shnider SM et al: Dopamine administration in the normotensive pregnant ewe. Obstet Gynecol 51:586-589, 1978)*

Pulmonary Vascular Response to Sodium Nitroprusside in Anesthetized Dogs

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The influence of sodium nitroprusside (SNP) infusion on pulmonary hemodynamics and total calculated pulmonary vascular resistance was examined in chloralose anesthetized, spontaneously breathing, normoxic and hypoxic closed-chest dogs previously instrumented to record pulmonary arterial pressure and flow. Dose-response curves for pulmonary and systemic vascular resistance were determined in the control state and at each of 7 doses of SNP administered as a continuous IV infusion. Dose-response data were determined before and after sympathetic blockade with propranolol and phentolamine. Prior to sympathetic blockade, systemic arterial pressure and calculated systemic vascular resistance decreased progressively with the dose of SNP. Following autonomic blockade, the fall in systemic arterial pressure was enhanced while systemic vascular resistance declined further. In contrast to the systemic circulation, pulmonary vascular resistance tended to increase progressively with the dose of SNP, rising from 4.21 (± 0.5 SEM) to a maximum of 5.02 (± 0.48 SEM) mm Hg/ml/min .10^{-2}. Following sympathetic blockade, pulmonary vascular resistance increased further during SNP infusion, rising from 4.79 (± 0.64 SEM) to 6.40 (± 1.1 SEM) mm Hg/ml/min .10^{-2}. Changes in pulmonary vascular resistance were not significantly affected by sympathetic blockade. On the other hand, infusion of SNP during conditions of enhanced pulmonary vasoconstriction induced by breathing 5% O_2 resulted in a significant fall in pulmonary arterial mean pressure and a significant decrease in calculated vascular resistance.

It is concluded that, in the normal lung, SNP may alter pulmonary vascular resistance via extrinsic mechanisms arising from the associated fall in mean left atrial pressure and venous return, whereas in the hypoxic vasoconstricted lung the predominant effect is a reduction in mean pulmonary arterial pressure and a decrease in total pulmonary vascular resistance due to direct pulmonary vasodilatation.

Key Words—LUNG, pulmonary vasculature. ANESTHETIC TECHNICS, induced hypotension, nitroprusside.

THE increasing application of vasodilator agents in the treatment of acute cardiovascular disorders has stimulated several studies designed to evaluate the physiological and pharmacological activity of these substances. Among the several vasodilator agents currently available, sodium nitroprusside (SNP) has found widespread application in the treatment of hypertensive crisis, congestive failure, and myocardial infarction.[1-6] The salutary effect of this agent on left ventricular function resides in its ability to reduce ventricular afterload and decrease systemic vascular resistance.[2-5] The pharmacological basis for this response arises from direct relaxation and vasodilatation of vascular smooth muscle.[7,8]

The responses of the pulmonary circulation to SNP are less clearly defined. Studies indicate that SNP may decrease pulmonary arterial pressure and reduce pulmonary vascular resistance.[5,9] Pulmonary vasodilatation has been suggested as an explanation for the fall in arterial Po_2 observed during SNP infusion during general anesthesia.[10-13] It has been postulated that SNP may decrease arterial Po_2 by dilating pulmonary vessels hypoxically vasoconstricted in underventilated areas of the lung, leading to ven-

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tilation perfusion abnormalities.[10,11,13] However, definitive information concerning the effects of SNP in normal and hypoxic lung is lacking.

In order to accurately define the effects of SNP on normal and hypoxically vasoconstricted lung, experiments were performed on anesthetized closed-chest dogs under normoxic conditions and during systemic hypoxia. Furthermore, to evaluate the role of the sympathetic nervous system in the vascular response to SNP, the effects of SNP were evaluated before and after adrenergic blockade.

METHODS

Animal Preparation.—Experiments were performed on mongrel dogs of either sex (average weight, 18.3 kg ± 1.85 SD). Prior to study, the animals were instrumented to record pressure and flow. Under pentobarbital anesthesia (30 mg/kg IV), a thoracotomy was performed in the third interspace. The pericardium was opened and a wide bore catheter was secured in the left atrium through an incision in the appendage and the tip was positioned in the left atrial chamber. Next, the main pulmonary artery was dissected free from connective tissue for placement of an electromagnetic flow probe. Prior to implantation, the probes were calibrated, using whole blood. Pulmonary arterial pressure was recorded through a polyethylene catheter positioned in the main pulmonary artery 1 cm proximal to the flow probe via direct arterial puncture, employing the Seldinger technic. The chest was closed and the flow-probe connector was exteriorized. The pulmonary arterial and left atrial pressure catheters were brought out of the chest and positioned in a subcutaneous pocket. The animals were allowed to recover for 2 to 3 weeks before study. At the time of study the animals were anesthetized with chloralose (100 mg/kg IV). Systemic arterial blood pressure was measured through a catheter placed in a femoral artery and advanced into the thoracic aorta at the time of study. The femoral vein was catheterized for drug infusion. Pulmonary blood flow was measured with an electromagnetic flowmeter (CME Model #501). Pressure and flow pulses were recorded on an Offner Type R Dynograph.

Experimental Protocol.—Studies were performed with the animals lying supine on their right sides, breathing room air, with tracheal intubation. Solutions of SNP were prepared at the time of study from vials containing the crystalline compound. The solutions were shielded from light throughout the experiment. The influence of SNP on heart rate (HR), mean systemic arterial pressure (MSAP), pulmonary arterial systolic pressure (PASP), pulmonary arterial diastolic pressure (PADP), pulmonary arterial mean pressure (PAMP), left atrial mean pressure (LAMP), mean pulmonary blood flow (PAM$\dot{Q}$), maximum pulsatile pulmonary blood flow (Max P$\dot{Q}$), right ventricular stroke volume (SV), pulmonary vascular resistance (PVR), and systemic vascular resistance (SVR) were determined on a dose-response basis for each variable at each of the following infusion rates: 30, 42, 60, 85, 125, 185, and 270 μgm/min. The order of infusion was not randomized. Since the variability in animal weight was not great, the dose of sodium nitroprusside was expressed per kilogram of average body weight in the grouped data (fig 1, 2, and 3). Pressure and flow were plotted as a function of the dose of SNP expressed as the $\log_{10}$ of the infusion rate in μgm/kg/min. The average dose ranged between 1.6 and 14.8 μgm/kg/min at the first and final infusion rate, respectively. Each new dose rate was maintained until pressure and flow had stabilized before recording a new set of data.

In order to evaluate the contribution of the sympathetic nervous system to hemo-

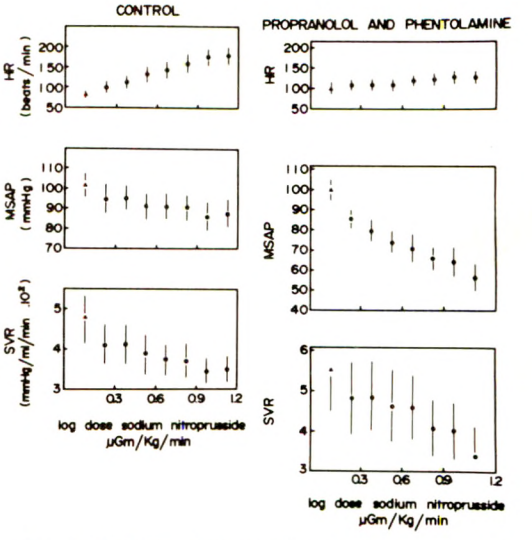


FIG 1. Sodium nitroprusside dose-response data for systemic circulatory parameters. Each point represents the average absolute value for a given parameter, with the associated vertical line representing 1 SEM. Data points were generated from 9 animals in the control and from 6 animals treated with phentolamine and propranolol.

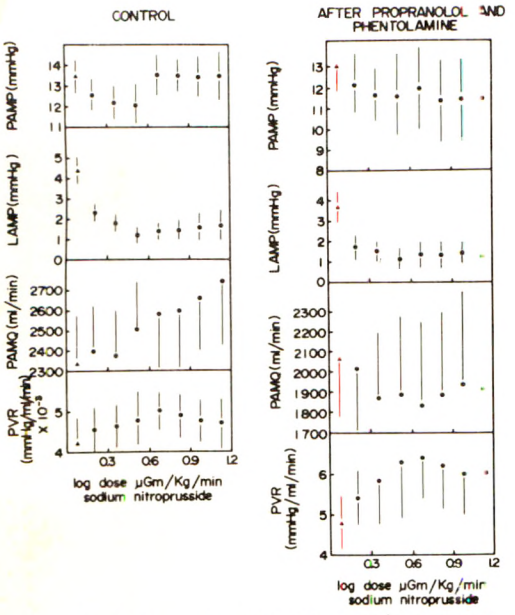


FIG 2. Sodium nitroprusside dose-response data for mean pulmonary circulatory parameters. Data treatment as in fig 1. The values of PVR were not significantly different from control values ($p>0.05$) either before or after sympathetic blockade.

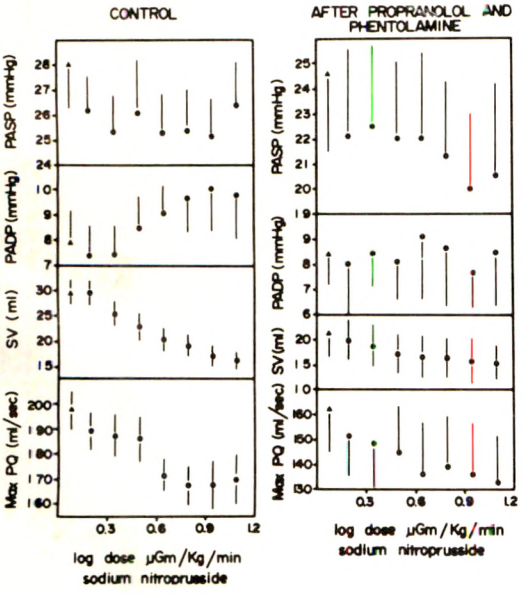


FIG 3. Sodium nitroprusside dose-response data for pulsatile pressure and flow. Data treatment as in fig 1.

dynamic responses, propranolol (1.0 mg/kg IV) and phentolamine (1.0 mg/kg IV) were administered in 6 animals and SNP dose-response curves determined before and after the administration of these drugs. Infusion of SNP was begun immediately following administration of each drug when hemodynamics had stabilized.

In 4 normoxic spontaneously breathing chloralose-anesthetized animals, arterial blood gases and pH were measured together with respiratory rate and depth both before and after propranolol and phentolamine at a low (2.4 µgm/kg/min) and high (15 µgm/kg/min) dose of SNP. Respiratory rate and depth were measured with an esophageal balloon.

In 5 additional animals, the effects of SNP were examined during systemic hypoxia induced by breathing hypoxic gas (5% O_2 and 5% CO_2) from a Douglas bag. After hemodynamic stabilization, a single dose of SNP was infused (approximately 9.2 µgm/kg/min) during systemic hypoxia. Blood-gas analysis was performed on arterial samples in the control and during hypoxia. Hemodynamic measurements were made in the control during hypoxia and during hypoxia plus SNP infusion.

Data Analysis.—Total PVR was calculated as the difference between PAMP and LAMP divided by PAMQ̇. Systemic vascular resistance was expressed as the ratio of mean aortic pressure to PAMQ̇. Pressure and flow data were obtained during the steady state at each of 7 rates of SNP infusion. Because of fluctuations during inspiration and expiration, pressure and flow waves were selected for analysis during the expiratory period. Data from 5 to 8 consecutive pulses were averaged for each level of SNP infusion. Each variable was plotted as the average absolute value plus or minus one SEM.

Statistical significance was determined using Student's *t*-test for paired data. Statistical analysis was performed on SVR and PVR values only in the normoxic studies. Statistical evaluation was made between the control value of resistance and the value obtained at each dose level before and after adrenergic blockade. A p value equal to or less than 0.05 was accepted as statistically significant.

RESULTS

Figure 1 shows dose-response data for HR and systemic variables. Control heart rate prior to drug infusion was 81 (± 5 SEM) beats/min and increased progressively with increasing doses of SNP, attaining 178 (± 19 SEM) beats/min at the maximum dose. In contrast, after propranolol and

phentolamine, the HR increase was blunted, reaching 129 (± 12) beats/min at the maximum dose. Mean systemic arterial pressure decreased from 102 (± 6 SEM) mm Hg in the control to 88 (± 6 SEM) mm Hg at the maximum dose of SNP. Mean systemic arterial pressure decreased even further during SNP infusion after propranolol and phentolamine, falling from 100 (± 13 SEM) mm Hg prior to infusion to 56 (± 6 SEM) mm Hg at the maximum dose. Similarly, SVR decreased progressively with the dose of SNP. Systemic vascular resistance decreased in control animals from 4.80 (± 0.6 SEM) mm Hg/ml/min $.10^{-2}$ to 3.52 (± 0.4 SEM) mm Hg/ml/min $.10^{-2}$ at the maximum SNP dose. This decrease was statistically significant ($p<0.01$). In like manner, after propranolol and phentolamine SVR decreased from 5.53 (± 1.1 SEM) mm Hg/ml/min prior to SNP infusion to 3.41 (± 0.7 SEM) mm Hg/ml/min at the maximum dose of SNP. This decrease was statistically significant ($p<0.01$).

Figure 2 shows dose-response data for pulmonary vascular mean pressure and flow and PVR. In the control, prior to drug infusion, PAMP was 13.5 (± 0.9 SEM) mm Hg. This remained essentially constant with increasing doses of SNP. On the other hand, LAMP decreased sharply at the lower dose levels of SNP, falling from 4.4 (± 0.7 SEM) mm Hg in the control prior to infusion to 1.2 (± 3 SEM) mm Hg at the third dose level. Mean pulmonary flow increased progressively and consistently with increasing dose of SNP, rising from 2333 (± 234 SEM) ml/min in the control to 2688 (± 308 SEM) ml/min at the maximum dose. Unlike SVR, PVR tended to increase with the dose of SNP; however, the values at each dose level were not statistically different from control ($p>0.05$). In the control state prior to drug infusion, PVR was 4.21 (± 0.5 SEM) mm Hg/ml/min $.10^{-3}$; it increased to a maximum of 5.02 (± 0.48 SEM) mm Hg/ml/min $.10^{-3}$ at the fourth dose level.

Following propranolol and phentolamine, PAMP decreased slightly from 13 (± 2 SEM) mm Hg prior to infusion of SNP to 12 (± 2 SEM) mm Hg at the maximum dose. Left atrial mean pressure decreased sharply with SNP from a control of 3.7 (± 0.8 SEM) mm Hg and stabilized at 1.1 (± 0.5 SEM) mm Hg. In contrast to the response before blockade, pulmonary flow tended to decrease progressively with the first 4 dose levels of SNP. This decline in pulmonary flow resulted in a greater change in PVR as compared with control before sympathetic blockade. Consequently, PVR increased from a control level of 4.79 (± 0.64 SEM) mm Hg/ml/min $.10^{-3}$ prior to infusion to 6.40 (± 1.1 SEM) mm Hg/ml/min $.10^{-3}$ at the fourth dose level; however, the values at each dose level were not statistically different from control ($p>0.05$).

Pulsatile pressure and flow changes during SNP infusion are shown in fig 3. Pulmonary arterial systolic pressure tended to decrease as the dose of SNP increased. This response was enhanced after propranolol and phentolamine. Conversely, PADP increased progressively with dose in the control; however, PADP remained unchanged from the preinfusion levels during SNP infusion after propranolol and phentolamine. Similarly, SV diminished progressively with SNP dose, but the rate of fall and the absolute change were attenuated after sympathetic blockade. Maximum pulsatile pulmonary flow decreased with the rate of infusion of SNP both in the control and after propranolol and phentolamine.

Table 1 summarizes systemic arterial blood gases and arterial pH along with respiratory rate and depth during SNP infusion in normoxic dogs before and after propranolol and phentolamine. The low dose of SNP was without effect on blood gases and respiratory rate and depth. Sodium nitroprusside infusion at the high dose was associated with a slight reduction in Po_2 both before and after sympathetic block. These changes in Po_2 were not statistically significantly different from control values. Respiratory rate and depth were unaffected at the high dose level. These data indicate that the administration of SNP did not change blood gases sufficiently to secondarily alter the hemodynamic responses of the normoxic animal model employed in this study.

Table 2 summarizes responses of mean pulmonary and systemic pressures, mean pulmonary flow, and pulmonary and systemic vascular resistance in 5 animals before and during systemic hypoxia, and during systemic hypoxia plus SNP infusion. Average blood-gas values in the control were Po_2 88 mm Hg, Pco_2 37 mm Hg, and pH 7.38. Average values during hypoxia were Po_2 34 mm Hg, Pco_2 30 mm Hg, and pH 7.39. Systemic hypoxia produced an increase in PAMP and PVR while SVR declined. The administration of SNP during systemic hypoxia resulted in significant

TABLE 1
Systemic Arterial Blood Gases During Sodium Nitroprusside Infusion in Normoxic Dogs

pH	P_{CO_2} (mm Hg)	P_{O_2} (mm Hg)	$\triangle Ep$ (mm Hg)	RR (breaths/min)	MSAP (mm Hg)
		Control			
7.42 ± 0.03	35 ± 4	92 ± 8	2.6 ± 1.0	16 ± 8	105 ± 15
		SNP 2.4 μg/kg/min			
7.42 ± 0.02	34 ± 5	90 ± 6	2.5 ± 0.8	18 ± 8	100 ± 18
		SNP 15 μg/kg/min			
7.40 ± 0.02	34 ± 3	84 ± 11	2.5 ± 0.9	18 ± 6	80 ± 13
		Control After Propranolol and Phentolamine			
7.43 ± 0.03	32 ± 3	91 ± 12	2.3 ± 0.7	20 ± 6	97 ± 15
		SNP 2.4 μg/kg/min			
7.43 ± 0.04	31 ± 2	92 ± 9	2.0 ± 0.6	20 ± 6	88 ± 6
		SNP 15 μg/kg/min			
7.42 ± 0.07	30 ± 5	86 ± 9	2.5 ± 0.5	20 ± 6	65 ± 9
		Control			
7.41 ± 0.04	32 ± 1	97 ± 23	2.3 ± 0.5	18 ± 6	108 ± 20

Data showing effects of a small and large dose of SNP on systemic arterial blood gases and respiratory function. Values indicate means ± 1 SD for 4 dogs. $\triangle Ep$ = absolute change in esophageal pressure; RR = respiratory rate.

TABLE 2
Pulmonary Vascular Response to Nitroprusside During Hypoxia

Group	PAMP (mm Hg)	LAMP (mm Hg)	$\dot{Q}$ mean (ml/min)	MSAP (mm Hg)	PVR (mm Hg/ml/min)	SVR (mm Hg/ml/min)
Control	12.2 ± 2.4	2.3 ± 2.3	2926 ± 297	111 ± 10	3.39 ± 0.32	3.84 ± 0.56
Hypoxia	20.7 ± 3.2 ($p<0.01$)	2.1 ± 2.0 (NS)	3484 ± 611 (NS)	120 ± 14 (NS)	5.52 ± 1.5 ($p<0.05$)	3.50 ± 0.50 (NS)
Hypoxia + SNP	14.1 ± 2.9 ($p<0.01$)	1.4 ± 1.5 (NS)	3176 ± 484 (NS)	83 ± 26 ($p<0.05$)	4.10 ± 0.56 ($p<0.05$)	2.54 ± 0.59 ($p<0.01$)

Data showing pulmonary and systemic vascular responses to systemic hypoxia before and during SNP infusion. Statistical analysis using Student's *t*-test for paired data was applied to determine the level of significance between control and hypoxia and between hypoxia and hypoxia plus SNP. *p* values are shown in parentheses.

reductions in PAMP, PVR, and SVR ($p<0.05$).

DISCUSSION

The results of this study indicate that SNP is essentially without effect on the pulmonary vasculature in the normoxic state. On the other hand, SNP diminished SVR in a dose-dependent fashion. Sodium nitroprusside exerts no direct effects on myocardial contractility[14,15] and, therefore, alterations in cardiovascular function during infusion of SNP can be attributed to its peripheral vascular effects together with modifications arising from reflex activation of the autonomic nervous system. Prior to propranolol and phentolamine, SNP infusion elicited a moderate fall in MSAP together with a rise in cardiac output. Following autonomic blockade, MSAP decreased to a greater extent during infusion and the HR response was attenuated. The increase in HR in the absence of autonomic blockade probably reflects baroreceptor mediated compensation for the fall in MSAP. The increase in cardiac output (mean pul-

monary flow) developed as a result of the increase in HR, since the flow increment was blocked together with an attenuation in HR following sympathetic blockade (fig 1 and 2). In addition, the fall in MSAP was enhanced following propranolol and phentolamine, suggesting that an increase in reflex sympathetic activity to systemic arterioles antagonized the direct vasodilator action of SNP.[7] Hence, HR and MSAP responses were substantially modified by the sympathetic nervous system during SNP infusion.

In contrast to SVR, PVR tended to increase with the dose of SNP; however, this change was not statistically significant. Nevertheless, this effect might be interpreted as indicating an increase in vasomotor tone arising from reflex pulmonary vasoconstriction. However, the increase in resistance persisted after sympathetic blockade, thus indicating that the rise in resistance was not the result of reflex pulmonary vasoconstriction induced via the alpha adrenergic system. It is doubtful that SNP produced direct pulmonary vasoconstriction, since PAMP decreased slightly rather than increased with increasing dose levels of SNP. Furthermore, it is unlikely that SNP would have an excitatory affect on pulmonary vascular smooth muscle, since the mechanism of action of SNP appears to involve inhibition of calcium flux in smooth-muscle cells.[7]

On the other hand, the elevation in total calculated PVR may be the result of extrinsic hemodynamic influences operating to control LAMP. Sodium nitroprusside has been shown to produce relaxation of smooth muscle of both systemic arteries and veins.[7,14,16] Consequently, in normal circulation increased venous compliance together with generalized arteriolar vasodilatation results in a fall in MSAP and a reduction in venous return. These changes cause LAMP to decline. A decrease in LAMP to near zero may allow pulmonary veins to reduce their caliber by decreasing distending pressure, resulting in a slight increase in calculated total PVR.[17-19] This observation differs from that of Rowe and Henderson, who demonstrated a 27% decrease in PVR in normal dogs receiving SNP.[9] However, in their study no values for LAMP are presented, and calculation of vascular resistance without this variable may have lead to erroneously low values for calculated resistance during SNP infusion.

In contrast to the normal lung, the administration of SNP during hypoxic pulmonary vasoconstriction resulted in a fall in PAMP and a decline in PVR. This observation indicates that SNP dilates hypoxically vasoconstricted pulmonary vessels, and therefore helps to explain the fall in arterial Po_2 observed in patients receiving SNP during general anesthesia. In this respect, Wildsmith et al found that the decrease in Po_2 was directly related to age as well as to the degree of pulmonary parenchymal disease in patients receiving SNP during operation.[13] They postulated that SNP dilated hypoxically constricted areas of the lung, causing imbalance in ventilation:perfusion ratios. Similarly, Colley and Cheney demonstrated that SNP may result in a profound reduction in arterial Po_2 when administered to dogs with extensive pulmonary atelectasis.[10] An average fall in Po_2 from 134 to 77 mm Hg was associated with an increase in the shunt:flow ratio, reflecting a reversal of hypoxic pulmonary vasoconstriction. The experiments in the present study indicate that SNP has the potential to reverse hypoxic pulmonary vasoconstriction and therefore to establish the physiological bases for interpretation of blood-gas alterations during the administration of this drug.

In conclusion, over a large range of doses, SNP is essentially without effect on pulmonary vascular vasomotor tone in the normal lung. Under the conditions of this study, fluctuations in PVR in the normal lung may be explained as associated alterations in pulmonary venous pressure arising from the systemic vascular effects of SNP. On the other hand, the administration of SNP to hypoxic vasoconstricted lung results in a direct pulmonary vascular vasodilatation and a fall in pulmonary vascular resistance.

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MORPHINE USE IN TETANUS

Cardiovascular dysfunction is a well-recognized complication of generalized tetanus ...an. Intravenous morphine was used to control autonomic hyperactivity producing ...ertension in a 43-year-old previously healthy patient with severe tetanus, requiring ...ilatory support. The hypertension had not been controlled by use of an alpha-...renergic blocking agent. Morphine dosage was 1 mg/kg initially, given during 15 ...inutes, followed by 1 to 2 mg/kg per 12-hour period. The average daily dose of ...morphine over a 22-day period was 140 mg. The authors suggest that morphine may offer advantages over adrenergic blocking agents in the treatment of autonomic hyperactivity in tetanus. *(Rie MA, Wilson RS: Morphine therapy controls autonomic hyperactivity in tetanus. Ann Intern Med 88:653-654, 1978)*

Naloxone Fails to Antagonize Thiopental Anesthesia

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A study was undertaken to determine the effect in man of naloxone on the central nervous system depression produced by IV thiopental. Eight normal volunteers were given 5 mg/kg thiopental IV. On a separate occasion the same 8 volunteers were given 50 μg/kg naloxone IV 5 minutes prior to 5 mg/kg thiopental. Naloxone had no significant effect on the rate of return of consciousness following administration of thiopental. Naloxone also had no significant effect on the responses of blood pressure, heart rate, or respiratory rate to thiopental.

Key Words — ANTAGONISTS, narcotic, naloxone. ANESTHETICS, intravenous, thiopental.

In rats 1 mg/kg naloxone administered subcutaneously or intraperitoneally significantly delays the onset of and decreases the duration of the loss of righting reflex produced by 35 mg/kg pentobarbital or methohexital administered by the same route.[1] Naloxone also decreases the toxicity of 50 to 125 mg/kg pentobarbital intraperitoneally administered and increases the LD 50 of pentobarbital from 59 to 101 mg/kg.[1] Moreover, in comatose patients naloxone antagonizes central nervous system depression caused by diazepam[2] and the combination of barbiturate, alcohol, and diazepam.[3]

The aim of this study was to determine whether naloxone could also counteract the central nervous system depressant effects of thiopental in humans.

METHOD

Four male and 4 female anesthesiologists in good health (ASA classification 1) were used as experimental subjects. Institutional approval of the investigation and informed consents were obtained.

Preliminary Study—A preliminary test was made in a conscious subject, weighing 80 kg, to determine possible adverse side effects of the large dose of naloxone we intended to use in the definitive studies. For this purpose 4.0 mg naloxone was injected via an IV infusion of 5% dextrose containing 0.2% NaCl running into a vein on the dorsum of a hand. The naloxone injecti[redacted] was made over 60 seconds, with the s[redacted] in the supine position. On the follo[redacted] 8.0 mg naloxone was injected in [redacted] manner using the contralateral hand[redacted] site of the infusion.

Blood pressure and heart and respira[redacted] rates were measured prior to the naloxo[redacted] injections and at frequent intervals over the ensuing 15 minutes. During this period of observation the ECG was monitored continuously.

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Definitive Study—In each of the 8 subjects an IV infusion of 5% dextrose containing 0.2% NaCl was established on the dorsum of the left hand. Blood pressure, heart rate, respiratory minute volume (using a Wright Respirometer and face mask), and respiratory rate were measured 10 minutes and immediately before and 2, 5, 8, 10, 15, 20, and 30 minutes after zero time. The level of consciousness of the volunteers was also evaluated at these same times by noting response to a painful stimulus (pressure applied over tip of mastoid process) and the ability to answer questions (eg, to give their correct telephone number on request). The ECG was monitored until 30 minutes after zero time.

The 4 male subjects received glycopyrrolate 0.2 mg IV 10 minutes before zero time, after control observations were made; at zero time, thiopental 5 mg/kg IV was given in 60 seconds. At least one week later each of the same 4 subjects was again given glycopyrrolate and thiopental but, in addition, naloxone 50 μg/kg IV was given in 60 seconds 5 minutes before zero time. The 4 female subjects received the same sequence of naloxone and thiopental and at least one week later thiopental without preceding naloxone.

Data were analyzed for statistical significance using a paired *t*-test.

RESULTS

Preliminary Study—During the injection of 4 mg naloxone an aching pain was experienced in the ipsilateral upper arm. Subsequent injection of 8 mg naloxone was made with the IV infusion running rapidly. Again pain was experienced in the ipsilateral arm but it was less severe. After these injections a warm feeling was experienced in the back and the conjunctivae, which became injected 4 and 7 minutes after zero time, respectively. The subject was able to sit and stand after the smaller and larger naloxone injections at 7 and 11 minutes, respectively.

After both naloxone injections a feeling of detachment and grogginess was experienced and physical activity required a conscious effort. These symptoms lasted for the remainder of the day and were more pronounced after 8 mg naloxone.

Cardiovascular vital signs before and after administration of naloxone are summarized in table 1. Blood pressure and heart rate were unaffected by either dose of naloxone. Respiratory rate and ECG were also unaffected.

Definitive Study—The ages and weights of the 8 subjects and the doses of thiopental and naloxone given to each are shown in table 2. The effects of naloxone on cardiovascular vital signs and respiratory measurements are shown in tables 3 and 4. There were no significant changes between the corresponding sets of data obtained at the same times, except that after naloxone, heart rate was faster between 5 and 15 minutes and respiratory rate was faster 5 minutes after zero time. Brief periods of apnea, however, lasting up to 40 seconds, except in one subject where it was 50 and 60 seconds, immediately followed the thiopental injections, whether or not naloxone had also been given. The duration of apnea on each occasion was about the same for the same subject. The subjective and objective pattern of loss of consciousness were characteristic for each subject; one subject, for example, laughed, another yawned, and in another the eyelids twitched.

Typically subjects reacted to a painful stimulus 2 minutes after the thiopental had been given. The times at which subjects were able to give their telephone numbers are shown in table 5. Naloxone had no significant effect on these times.

TABLE 1

Cardiovascular Vital Signs Before and After Naloxone Administration

Vital signs	Naloxone dose (mg)	Control values	Range after naloxone	
			Low	High
Systolic blood pressure	4	124	126 (3)*	140 (7)
	8	120	120 (11)	124 (3, 7, 9)
Diastolic blood pressure	4	80	80 (1, 3)	92 (10)
	8	70	80 (3, 7, 11)	90 (9)
Heart rate	4	60	54 (3)	78 (9)
	8	60	60 (3, 7)	70 (11)

*Numbers in parentheses are minutes after zero time.

TABLE 2
Subject Data and Drug Dosage

Subject	Age	Weight (kg)	Thiopental (mg)	Naloxone (mg)
1 (M)*	46	70	350	3.50
2 (M)	50	80	400	4.00
3 (M)	34	66	330	3.30
4 (M)	32	72	360	3.60
5 (F)	42	45	225	2.25
6 (F)	28	50	250	2.50
7 (F)	44	51	255	2.55
8 (F)	33	57	285	2.85
Mean ± SEM	38.6 ± 2.78	61.4 ± 4.39	306.9 ± 22.0	3.07 ± 0.22

*Letters in parentheses denote sex.

As in the preliminary study, pain was experienced in the arm on the side of the IV infusion during and shortly after the naloxone injection. Conjunctival injection was noted and a feeling of slight pressure around the eyes was experienced 2 to 4 minutes after naloxone. There were no ECG abnormalities.

Characteristically there was less euphoria and loquacity after thiopental when this was preceded by naloxone. After thiopental alone, subjects tended to remain awake after they regained consciousness. In contrast, when naloxone had been given they lapsed back to sleep after answering questions both during the initial 30-minute study period and for varying periods in the remainder of the day. Also after naloxone a feeling of detachment was present during the recovery period. The time taken to feel completely normal varied considerably from subject to subject, as shown in table 6.

DISCUSSION

This is the first report on possible CNS effect and of large doses of naloxone on circulatory and respiratory changes in healthy normal humans. In fact there were no changes in vital signs of any consequence after 50 μg/kg naloxone in the 8 subjects studied nor after 100 μg/kg in the preliminary study made in one conscious subject. The only other report in which a larger amount of naloxone was administered involved a study of male narcotic addicts in which one subject received 10 mg naloxone IV.[4]

The anticipation that naloxone might significantly decrease the effects of IV administered thiopental was not borne out in these studies even though a dose 10 times that considered appropriate for usual therapeutic purposes was used. Consequently, the use of naloxone in humans as an antagonist to thiopental does not appear warranted. The recovery period was generally less pleasant when naloxone was given prior to thiopental. Furthermore, the characteristic feeling of detachment and grogginess experienced after the relatively large doses of naloxone could be hazardous in the recovery period during ambulation or driving an automobile.

The findings of this study emphasize the fact that anesthesia produced by thiopental in humans is neurochemically or neuropharmacologically different from anesthesia produced by inhalation anesthetics[5-7] or barbiturates[1] in rodents. The authors of these studies[1,5-7] have hypothesized that, in view of the effect of naloxone on inhalation anesthetics and barbiturates in animals, such anesthesia may involve CNS endorphines. Our data clearly demonstrate that thiopental effect is not mediated by CNS endorphines in humans. Furthermore, our data indicate that thiopental differs from other nonnarcotic IV CNS depressants such as diazepam which can be antagonized by naloxone.[3]

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TABLE 3

Effect of Naloxone on Cardiovascular Vital Signs

Parameters	Drugs	Controls 1st	Controls 2nd	Minutes after zero time 2	5	8	10	15	20	30
Systolic blood pressure	Thiopental	119.0 ± 3.30[1]	123.4 ± 4.47	124.8 ± 5.99	122.8 ± 4.98	120.0 ± 3.51	118.8 ± 3.56	117.8 ± 2.96	115.8 ± 2.52	116.6 ± 3.65
	Naloxone + thiopental	125.3 ± 2.90	124.8 ± 3.05	124.0 ± 4.33	120.8 ± 3.50	122.0 ± 2.93	121.5 ± 1.76	117.6 ± 2.43	116.3 ± 2.52	113.6 ± 2.90
Diastolic blood pressure	Thiopental	70.3 ± 4.17	71.0 ± 4.36	74.0 ± 5.58	70.8 ± 4.78	70.8 ± 4.07	70.8 ± 4.05	68.5 ± 3.83	70.3 ± 3.10	70.8 ± 4.05
	Naloxone + thiopental	76.8 ± 3.62	75.8 ± 3.47	78.8 ± 5.13	76.3 ± 4.04	75.0 ± 3.42	76.3 ± 2.63	73.6 ± 3.22	71.5 ± 3.06	74.0 ± 3.64
Heart rate	Thiopental	77.1 ± 4.88	79.8 ± 5.12	90.1 ± 3.47	84.8 ± 3.96	79.9 ± 3.87	77.8 ± 4.13	72.9 ± 4.70	75.3 ± 4.79	74.5 ± 5.22
	Naloxone + thiopental	81.8 ± 6.71	84.8 ± 6.65	99.1 ± 5.12	94.4 ± 4.49†	89.1 ± 4.45*	85.5 ± 5.38*	84.4 ± 5.98‡	80.4 ± 5.63	77.5 ± 4.82

[1]Mean ± SEM of 8 experiments

*, †, and ‡ indicate significant increases $p<0.05$, $p<0.01$, and $p<0.005$ respectively.

TABLE 4

Effect of Naloxone on Respiratory Measurements

Parameters	Drugs	Controls 1st	Controls 2nd	Minutes after zero time 2	5	8	10	15	20	30
Minute ventilation (l)	Thiopental	6.8 ± 0.74[1]	6.9 ± 0.67	4.8 ± 0.91	5.1 ± 0.88	5.4 ± 1.07	5.6 ± 0.70	5.3 ± 0.53	5.3 ± 0.62	5.4 ± 0.86
	Naloxone + thiopental	6.6 ± 0.61	6.9 ± 0.64	4.9 ± 0.85	5.2 ± 0.75	5.3 ± 0.76	5.7 ± 0.66	5.6 ± 0.79	5.1 ± 0.81	4.9 ± 0.69
Respiratory rate	Naloxone	11.3 ± 1.03	12.0 ± 1.13	11.1 ± 2.33	13.1 ± 1.42	13.3 ± 1.32	13.0 ± 1.12	10.8 ± 1.00	10.0 ± 1.21	9.5 ± 0.82
	Naloxone + thiopental	11.8 ± 0.94	11.5 ± 0.93	13.5 ± 2.17	15.6 ± 1.16*	14.8 ± 1.68	14.0 ± 1.41	11.4 ± 1.02	9.8 ± 0.98	9.5 ± 0.78

[1]Mean ± SEM of 8 experiments

*Significant increase $p<0.05$.

TABLE 5
Effect of Naloxone on Duration of Unconsciousness After Thiopental

Subject	After thiopental alone	After naloxone and thiopental
1	6.50*	4.20
2	8.00	9.50
3	3.00	3.50
4	4.00	7.50
5	3.25	3.50
6	4.75	4.75
7	3.42	3.50
8	3.67	3.50
Mean ± SEM	4.57 ± 0.68	4.99 ± 0.80

*Minutes after zero time to say telephone number

TABLE 6
Hours After Zero Time to Feel Completely Normal

Subject	Thiopental alone	Naloxone and thiopental
1	>8.00*	4.00
2	9.50	>10.50*
3	3.30	1.50
4	72.00	24.00
5	2.50	7.00
6	2.00	7.00
7	4.00	10.58
8	3.75	5.75

*Did not feel normal upon retiring that evening

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PULMONARY EFFECTS OF ALBUMIN

The effect of albumin when added to the resuscitation regimen of patients in hypovolemic shock was studied in a randomized prospective manner in 52 injured patients who received an average of 15.3 transfusions, 9.6 l of balanced electrolyte solution, and 980 ml of fresh frozen plasma. Twenty-seven patients received an average of 25 g of albumin initially and 150 g/day for 3 to 5 days. Patients who received albumin had greater dependence on respiratory support, averaging 8 days compared with 3 days in patients not receiving albumin. Patients receiving albumin had forced inspiratory oxygen/Pao_2 ratios that were significantly higher than those of patients not receiving albumin. These effects were associated with increased plasma volumes caused by the oncotic effects of albumin and by its interference with saline diuresis. In the circumstances studied, albumin appeared to have a detrimental effect on respiratory function. *(Weaver DW, Ledgerwood AM, Lucas CE, et al: Pulmonary effects of albumin resuscitation for severe hypovolemic shock. Arch Surg 113:387-392, 1978)*

Comparison of Dezocine (WY 16, 225) and Meperidine as Postoperative Analgesics

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The efficacy and safety of dezocine, 5 and 10 mg, were compared in a double-blind study to meperidine, 25 and 50 mg, when administered IM for relief of postoperative pain in the recovery room. One hundred and three patients (Group I) received no narcotic as preanesthetic medication while 84 did (Group II). The number of patients complaining of severe postoperative pain was significantly greater ($p<0.001$) in Group I than in Group II. Among patients in Group I complaining of severe pain, dezocine 10 mg was significantly more analgesic ($p<0.01$) than meperidine 25 mg for the first hour after injection and at least as effective as meperidine 50 mg. Data for the 23 patients in Group I complaining of moderate pain and those with severe pain who remained in the study after the first hour were insufficient to analyze statistically because of the small number in each group of patients.

The analgesia produced by either dose of dezocine or meperidine was not statistically different in patients in Group II complaining of either moderate or severe pain. However, there was a trend showing better pain relief with the higher dose of each drug.

Changes in degrees of sedation, vital signs, and side effects were similar among the groups.

We conclude that dezocine 10 mg is as effective as meperidine 50 mg for the relief of postoperative pain.

Key Words—ANALGESICS, dezocine. ANALGESICS, meperidine. PAIN, postoperative.

Opioid antagonist analgesics are expected to produce fewer side effects and to have a lower addiction liability than opioid analgesics. Some of the opioid antagonist analgesics, eg, R & S 218-M,[1] meptazinol,[2] buprenophine,[3] and pentazocine,[4] have been studied in the last decade, but only the latter is available in the United States. Pentazocine also has psychotomimetic side effects and produces dependence.[5]

Dezocine, a new synthetic narcotic antagonist and analgesic, is compared structurally to pentazocine (fig). The pH of a 2%

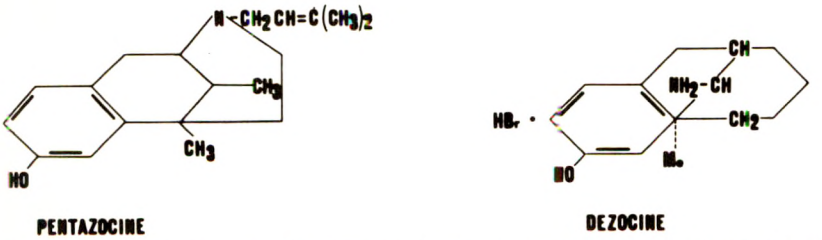


FIGURE. The structural formula for dezocine, (-)-13-beta-amino-5,6,7,8,9,10,11,12-octahydro-5 alpha-methyl-5, 11-methanobenzocyclodecen-3-ol, hydrobromide is compared to that of pentazocine.

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aqueous solution of dezocine is 4.6. Its potency as an antagonist against morphine in rats is 0.56 times that of nalorphine. Preliminary studies suggest that dezocine is similar to morphine in potency and duration of action.*

We compared, in a double-blind study, 2 dose levels of dezocine, 5 and 10 mg, with meperidine, 25 and 50 mg, to determine differences in efficacy and safety when given IM for the relief of postoperative pain.

METHODS AND MATERIALS

One hundred and eighty-seven patients were studied after they were fully informed of the nature of the study and signed consent forms.† Patients were ASA physical status I and II, 18 to 60 years of age, weighed 45 to 90 kg, and were scheduled for elective pulmonary thoracic, general abdominal, gynecological, orthopedic, or urologic surgery. Patients who might be pregnant or who were taking narcotic drugs were not studied. Any anesthetic agent was allowed except droperidol. When patients awoke in the recovery room and complained of moderate or severe pain, they were given an IM injection from a coded, single-dose ampul. The injection was either 5 or 10 mg of dezocine or 25 or 50 mg of meperidine according to a table of random numbers. Patients scored pain relief as complete, greater than 50%, 50%, less than 50%, or none 15, 30, 60, 120, and 240 minutes after injection. At each interval the degree of sedation was rated as none, mild, moderate, or marked by a nurse observer (NC) who also recorded the pain-relief scores. Blood pressure, heart rate, and respiratory rate were recorded at each interval. Side effects were recorded during the 4-hour observation period and again the next day after interviewing the patient and reviewing the hospital chart. If 50% or greater pain relief was not achieved after 1 hour and if the patient requested another analgesic, a standard analgesic was administered and the patient's study terminated.

Analgesic drugs were eliminated as premedicants and during surgery in 103 patients (Group I). Eighty-four patients received narcotic premedication or were given IV narcotics during surgery (Group II).

*Personal communication, Walter H. Comer, MD, Wyeth Laboratories, Philadelphia, Pennsylvania

†This study was reviewed and approved by the Northwestern University–Northwestern Memorial Hospital Institutional Review Board.

The chi-square test was used to compare the initial pain intensity of each group. Kruskal-Wallis chi-square analysis corrected for ties[6] and Dunn's multiple comparisons analysis[7] were used to compare analgesia and sedation among the drug-dose groups. The Student *t*-test was used to analze demographic data and to compare blood pressure, heart rate, and respiratory rate with preinjection control measurements.

RESULTS

The age, height, weight, and distribution of surgical procedures were similar for patients in Group I and II with one exception. Patients in Group I complaining of severe pain who received meperidine 25 mg were significantly ($p<0.05$) heavier than those who received meperidine 50 mg (mean weight 70 kg compared to 60 kg).

The percentage of patients in Group I who had 50% or greater pain relief at time intervals up to 120 minutes after injection is shown in table 1. Dezocine 10 mg was significantly more analgesic than meperidine 25 mg at 15, 30, and 60 minutes and more analgesic than dezocine 5 mg at 30 minutes ($p<0.01$). Meperidine 50 mg was significantly more analgesic than meperidine 25 mg at 30 minutes ($p<0.01$) and at 60 minutes ($p<0.05$). Significant differences were not seen when meperidine 50 mg was compared to dezocine 5 mg although there was a trend showing better analgesia with meperidine 50 mg. The larger doses of the 2 drugs were similar to each other, as were the smaller doses. In Group I, the number of patients with moderate pain and those with severe pain remaining in the study after 1 hour were insufficient for statistical analysis.

In Group II, analgesic effectiveness was compared among the 40 patients who complained of moderate pain and the 44 who complained of severe pain (table 2). No significant differences in pain relief occurred among these patients.

In Group I, 23 patients complained of moderate pain and 80 of severe pain. In Group II, 40 patients complained of moderate pain and 44 complained of severe pain. Use of a narcotic for premedication significantly shifted the intensity of pain upon awakening from severe to moderate ($p<0.001$).

Degrees of sedation were similar among the patients in all groups. Clinically signifi-

TABLE 1
Percentage of Patients with 50% or Greater Pain Relief
Who Had No Prior Narcotic

	Severe pain			
	15 min	30 min	60 min	120 min
Dezocine 5 mg*	30	15	20	5
Dezocine 10 mg*	60	70	50	25
Meperidine 25 mg*	5	0	0	0
Meperidine 50 mg*	40	50	45	10

*$n = 20$

Statistical Comparisons of Groups by Dunn's Multiple Comparisons Analysis

	15 min	30 min	60 min
Dezocine 5 mg vs meperidine 25 mg	NS*	NS	NS
Dezocine 5 mg vs meperidine 50 mg	NS	NS	NS
Dezocine 10 mg vs meperidine 25 mg	$p<0.01$	$p<0.01$	$p<0.01$
Dezocine 10 mg vs meperidine 50 mg	NS	NS	NS
Dezocine 10 mg vs dezocine 5 mg	NS	$p<0.01$	NS
Meperidine 50 mg vs meperidine 25 mg	NS	$p<0.01$	$p<0.05$

*Not significant

TABLE 2
Percentage of Patients with 50% or Greater Pain Relief
Who Had Prior Narcotic

	Moderate pain				
	15 min	30 min	60 min	120 min	240 min
Dezocine 5 mg*	60	70	80	40	10
Dezocine 10 mg*	50	80	50	30	10
Meperidine 25 mg*	40	40	20	0	0
Meperidine 50 mg*	40	70	30	20	20

	Severe pain			
	15 min	30 min	60 min	120 min
Dezocine 5 mg†	27	27	27	0
Dezocine 10 mg†	27	45	54	9
Meperidine 25 mg†	9	27	27	27
Meperidine 50 mg†	36	36	36	9

*$n = 10$ †$n = 11$
No statistically significant differences are seen among the groups.

cant changes in blood pressure, heart rate, and respiratory rate were not seen during the observation period.

Side effects were similarly distributed among the drug-dose categories (table 3). Miscellaneous side effects after dezocine included facial flushing, diplopia, vertigo, and diaphoresis. Those after meperidine included dyspnea and petit-mal-like seizures in the extremities. All these miscellaneous side effects were transient single occurrences which required no treatment.

DISCUSSION

The inherent subjectivity in studies of the efficacy and safety of analgesic drugs in the

TABLE 3
Side Effects in All Patients

Side effect	Dezocine 5 mg	Dezocine 10 mg	Meperidine 25 mg	Meperidine 50 mg
Nausea without vomiting	3	4	3	3
Vomiting	2	5	2	5
Erythematous rash	1	0	0	2
Miscellaneous	2	2	0	2

No significant differences occurred among the groups.

early postoperative period after general anesthesia causes certain pitfalls. First, patients in this study were relating their pain intensity at each succeeding interval to that experienced initially. They could not distinguish the effects of a rising blood level of analgesic drug from the opposite effect of a declining blood level of general anesthetic agents. This might explain why few patients remained in the study longer than 2 hours (30/124 with severe pain and 28/63 with moderate pain). Second, the observed degree of sedation was related to the duration of anesthesia and could not be correlated with the analgesic response. Third, side effects, especially nausea and vomiting, could be due to general anesthetic agents, the surgical procedure, or physical manipulation of patients by recovery room personnel.

The results indicate that dezocine 10 mg and meperidine 50 mg produced approximately the same pain relief and duration of action in unpremedicated patients. Patients who received narcotic premedication showed no significant difference in drug effect at either dose level of either drug although there was a trend toward better relief with dezocine and the larger dose of meperidine. When the pain level was moderate initially, narcotic premedication appeared to enhance the effectiveness of the smaller doses of the 2 drugs, especially dezocine 5 mg. It eliminated the dose-response trend seen between both doses of dezocine in patients initially complaining of severe pain. Meperidine 25 mg was expected to have a placebolike effect. For ethical reasons, a true placebo was not used.

Narcotic premedication significantly decreased the number of patients complaining of severe postoperative pain but changed neither the effectiveness of the analgesics 30 minutes after injection nor the duration of their action.

In equianalgesic doses, dezocine appears to be at least as safe as meperidine since no differences were seen in the degree of sedation or the incidence of side effects. Other than nausea and vomiting, side effects were rare and of little consequence. Vital sign changes were not clinically significant in any group.

We conclude that the analgesic potency of dezocine 10 mg is at least that of meperidine 50 mg, but less than preliminary studies indicated. Psychotomimetic effects seen with pentazocine were not observed in this study. If its low addiction potential is borne out by further studies, dezocine would be a good alternative to meperidine.

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The Influence of Spinal and Epidural Anesthesia on Neutrophil Chemotaxis in Man

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In this study the effects of tetracaine spinal anesthesia with (Group II) and without (Group I) epinephrine and of lidocaine lumbar epidural anesthesia with (Group IV) and without (Group III) epinephrine on polymorphonuclear (PMN) and total white blood cell (WBC) counts and PMN chemotaxis were evaluated in 28 patients before, during, and after anesthesia and operation. Preanesthetic PMN and WBC counts and PMN chemotaxis were similar in all groups. Polymorphonuclear and WBC counts were unaffected by anesthetic technics and operation; however, significant increases in both PMN and WBC counts occurred in all four groups postoperatively, after anesthesia had worn off. Polymorphonuclear chemotaxis was not altered at any time in patients in Group I to III. In contrast, patients having epidural anesthesia with epinephrine experienced a significant decrease in PMN chemotaxis during anesthesia and operation which recovered to preanesthetic levels after anesthesia wore off postoperatively.

The data demonstrate that spinal anesthesia with or without epinephrine and epidural anesthesia without epinephrine do not influence PMN chemotaxis but that epidural anesthesia with epinephrine significantly impairs PMN chemotactic responses. The importance of these findings on the susceptibility to infection of patients anesthetized with epidural anesthesia plus epinephrine remains to be investigated.

Key Words—BLOOD, leukocytes.

Two recent reports from this laboratory have suggested that general anesthesia in man may impair polymorphonuclear neutrophil chemotaxis (the ability of the neutrophil to migrate toward a bacterial stimulus).[1,2] The influence of spinal or epidural anesthesia on neutrophil chemotaxis is unknown. In this study we measured the effects of spinal and epidural anesthesia with and without epinephrine on neutrophil chemotaxis in 28 patients undergoing a variety of urologic and gynecologic operations.

METHODS

Written informed consent was obtained from each patient at the time of the preoperative visit. Patients who had infection, extensive tumors, required blood transfusion, or sustained significant hypotension (a decrease in blood pressure of 35% or more) during or immediately after anesthesia and surgery were excluded from the study.

Premedication, 1.5 hours before operation, included either phenobarbital 1 mg/kg or diazepam 0.1 mg/kg, plus morphine 1 mg/10 kg and atropine 0.05 mg/10 kg. Blood, 9.5 ml, from a peripheral vein was obtained immediately prior to induction of anesthesia and added to 0.5 ml of a solution of beef lung heparin, 1000 μ/ml. Following this, an infusion of lactated Ringer's solution was started in an arm vein and standard blood

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pressure and precordial pulse-rate monitoring initiated. Patients were randomly divided into 4 groups of 7 with respect to anesthetic management. Groups I and II received tetracaine spinal anesthetics (8 to 12 ml of a 1% solution of tetracaine mixed with an equal volume of 10% dextrose in H_2O) in the lateral position at L_{4-5}. Group II patients had epinephrine 0.1 mg added to the anesthetic solution but Group I did not. Patients in Groups III and IV received a lidocaine "one-shot" lumber epidural anesthetic (19 to 24 ml of a 1.5% solution of lidocaine) in the lateral position at L_{3-4} or L_{4-5}. Group IV had epinephrine 0.2 mg added to the anesthetic solution; Group III did not.

Additional peripheral venous specimens were obtained after 40 minutes of anesthesia (without surgery), 20 minutes after the start of the operation (69 to 90 minutes after anesthesia), and 8 hours after performance of the spinal or epidural block, when all clinical evidence of anesthesia was gone. All blood specimens were also examined for leukocyte random migration and total and differential white blood cell (WBC) counts.

Leukocyte-Function Tests

Chemotaxis—Hill and coworkers' in vitro method[3,4] was used for studying chemotaxis. Leukocyte-rich plasma was obtained by allowing the erythrocytes in the 10-ml heparinized blood specimens to settle over a 1-hour period. After determination of the number of polymorphonuclear leukocytes (PMN's) in the leukocyte-rich plasma, 0.1 ml of the suspension was diluted to 0.4 ml with tissue-culture medium 199, and the cells were deposited on one side of a 5-μ pore-size Millipore filter using a Shandon sytocentrifuge.* The filters were immediately placed in a modified Boyden chamber† and the chemotactic stimulus was added to the attractant side. After incubation for 3 hours at 37 C, the migrant PMN's within the reticule of 10 random fields were counted (using a 10x ocular 45x objective and a 5x-5 mm photo reticule). The neutrophil chemotactic index was calculated by dividing the number of PMN's that had migrated through the filter by the total number of PMN's ($x10^6$) delivered to the starting side of the filter. The index, therefore, measures intrinsic neutrophil chemotactic activity. Neither percentage nor total number of mononuclear cells in the suspension affect the chemotactic index, and there is no association between the number of PMN's delivered to the filter and the chemotactic index. Chemotactic assays were made in triplicate.

Chemotactic Factor—A bacterial chemotactic factor was prepared from a culture filtrate of Escherichia coli grown in medium 199 for 24 hours at 37 C. After passage through an 0.2-μ Millipore filter, this factor was frozen at −70 C in 1-ml ampules. For each experiment, an ampule was thawed and diluted in medium 199, so that each millilitre of the solution contained 50 μl of the factor. Two millilitres of this solution were added to the bottom or attractant side of the chemotactic chamber for each analysis. The same lot of filtrate was used throughout the study.

Random Motion—Random motion of leukocytes was measured by determining the chemotactic index when no chemotactic stimulus was added to the attractant side of the modified Boyden chamber.

All data were examined for significance utilizing Student's paired *t*-test. Changes after anesthesia, during operation, and postoperatively (after recovery from anesthesia) were compared to preanesthetic control values in each group.

RESULTS

The 4 groups of patients were comparable with respect to age and weight and had operations of similar type and duration (table 1). Patients in Groups I and II received similar amounts of tetracaine; those in Groups III and IV similar amounts of lidocaine. Preanesthetically, PMN chemotaxis, random migration and counts, and WBC counts were also similar in the 4 groups (tables 2 and 3). Polymorphonuclear and WBC counts were unaffected by anesthesia or operation; however, significant increases in both neutrophil and total WBC counts occurred in all 4 groups postoperatively, after anesthesia had worn off.

Neutrophil chemotaxis was slightly decreased (7 to 11%) during anesthesia and operation and slightly increased postoperatively in patients in Groups 1 to 3. None of these changes were statistically significant, $p>0.30$. On the other hand, patients in Group IV experienced a significant $p<0.05$ decrease in neutrophil chemotaxis during

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TABLE 1
Preoperative and Intraoperative Data (Mean ± SD)

Group	I	II	III	IV
Age (years)	54 ± 12	58 ± 13	51 ± 11	53 ± 14
Weight (kg)	63 ± 9	67 ± 11	64 ± 10	66 ± 9
Duration of operation (min)	154 ± 37	168 ± 28	139 ± 31	145 ± 26
Tetracaine (mg)	9.9 ± 0.6	10.1 ± 0.5	. . . . .	. . . . .
Lidocaine (mg)	. . . . .	. . . . .	364 ± 33	378 ± 28

TABLE 2
Effects of Spinal and Epidural Anesthesia on White Blood Cell (WBC) and Polymorphonuclear (PMN) Counts (Mean ± SD)

	Group	Preanesthesia	Anesthesia	Anesthesia and operation	Postoperative
Total WBC (10^3 per mm^3)	I	8.3 ± 1.8	8.6 ± 2.1	8.9 ± 2.6	18.4 ± 3.8*
	II	8.5 ± 1.6	8.9 ± 2.0	8.9 ± 2.2	19.2 ± 3.6*
	III	8.5 ± 1.8	9.0 ± 1.8	9.0 ± 1.8	18.7 ± 4.0*
	IV	8.2 ± 1.4	8.5 ± 1.9	8.8 ± 1.9	17.9 ± 3.6*
PMN cell count (10^3 per mm^3)	I	4.0 ± 0.8	4.2 ± 1.1	4.4 ± 1.0	12.1 ± 1.5*
	II	3.7 ± 0.9	4.1 ± 0.7	4.4 ± 0.9	13.3 ± 1.6*
	III	3.9 ± 0.8	4.3 ± 0.9	4.3 ± 0.8	12.6 ± 1.3*
	IV	4.1 ± 0.7	4.3 ± 1.0	4.2 ± 0.9	12.8 ± 1.7*

*$p<0.05$, Student's paired t-test, when compared to preanesthetic values

TABLE 3
Effects of Spinal and Epidural Anesthesia on Leukocyte Chemotaxis and Random Migration (Mean ± SD)

Cell function	Group	Preanesthesia	Anesthesia	Anesthesia and operation	Postoperative
Chemotactic index	I	74 ± 13	71 ± 14	69 ± 12	83 ± 15
	II	76 ± 15	69 ± 12	68 ± 11	81 ± 13
	III	73 ± 12	67 ± 11	65 ± 9	84 ± 12
	IV	76 ± 14	55 ± 9*	58 ± 11*	87 ± 16
Random migration index	I	9.5 ± 2.4	9.4 ± 1.9	9.1 ± 2.1	9.6 ± 2.0
	II	9.1 ± 1.9	9.2 ± 1.8	8.9 ± 2.0	9.1 ± 2.6
	III	9.4 ± 2.2	9.0 ± 1.9	8.8 ± 2.3	9.3 ± 2.1
	IV	9.6 ± 2.0	9.2 ± 2.1	8.8 ± 2.4	9.7 ± 2.5

*$p<0.05$, Student's paired t-test, when compared to preanesthetic values

anesthesia (−28%) and operation (−25%), both of which returned to preanesthesia levels in the postoperative period. Neutrophil random migration was not significantly altered in any group during any of the experimental periods.

DISCUSSION

Rapid migration of neutrophils to an area of bacterial invasion is a critical factor in preventing infection.[5] Neutrophil chemotaxis is the mechanism by which PMN's are attracted to bacteria.[3,6] A number of investigations have shown that patients who do not experience an increase in PMN chemotaxis during early bacterial invasion have an increased susceptibility to severe infections.[7-10] Previous studies in this laboratory have demonstrated that general anesthesia with halothane, enflurane, or N_2O

plus narcotics significantly depresses neutrophil chemotaxis.[1,2] The results of the present investigation indicate that spinal anesthesia with or without epinephrine and epidural anesthesia without epinephrine produce no change in neutrophil chemotaxis during anesthesia and operation. Our findings suggest that patients subjected to epidural anesthesia with epinephrine may be more prone to bacterial infection than are patients anesthetized with spinal anesthesia or epidural anesthesia without epinephrine.

Hill and coworkers[11] have demonstrated that compounds with beta-adrenergic stimulation activity markedly impair PMN chemotaxis while those with alpha-adrenergic activity enhance the neutrophil response to the bacterial chemotactic factor. Although epinephrine plasma levels could not be measured during this study, our findings suggest that epinephrine may be present in the blood stream after epidural anesthesia with an epinephrine-containing solution in amounts adequate to significantly impair PMN chemotaxis. The data also indicate the lidocaine that appears in the blood stream following spinal or epidural anesthesia has no influence on PMN chemotaxis.

Surgical stress during general anesthesia with certain anesthetics and after all types of anesthesia is associated with increases in PMN and WBC counts, at a time when significant elevation in both epinephrine and norepinephrine occur.[1,2,8,12] Increases in PMN and WBC counts in the postoperative period in this study are comparable to those found after general anesthesia.[1,2] Recovery of PMN chemotaxis to preanesthetic levels in the postoperative period in patients in Group IV in this study is similar to the recovery found after general anesthesia. We have previously speculated that recovery of PMN chemotaxis after general anesthesia may be related to a preponderance of pain or stress-induced alpha rather than beta-adrenergic stimulation during the early postoperative period.[1] Increases in alpha-adrenergic stimulation might also explain recovery of PMN chemotaxis in patients in Group IV and the slight but insignificant increase of postoperative PMN chemotaxis in all groups above preanesthetic levels in this study. Whether a change in circulating catecholamine levels is the mechanism by which epidural anesthesia with epinephrine depresses PMN chemotaxis and whether postoperative pain returns PMN chemotaxis to control levels or above remain to be proven.

We used a concentration of epinephrine in our epidural anesthetic solution that was approximately 1:100,000. This is a common concentration in our institution, but perhaps somewhat higher than what is used at other institutions (1:200,000). Whether this explains the impaired chemotaxis observed and whether similar changes would occur with a 1:200,000 concentration of epinephrine is unknown. Whatever the mechanism, our data indicate that patients anesthetized with epidural lidocaine and epinephrine have PMN chemotactic indexes which if prolonged over a sufficient period of time have been shown to be associated with increased susceptibility to infections in nonanesthetized man.[7-10] Unfortunately, additional blood samples for PMN chemotaxis analysis were not obtained later on during the operation and in the early postoperative period. Therefore, our data do not establish how long PMN chemotaxis remained decreased in patients in Group IV. While it seems unlikely that a decrease in neutrophil chemotaxis for 70 to 90 minutes (as occurred in Group IV patients) is long enough to significantly affect infection rate, the effect of this duration of chemotaxis depression on infection rate has not been established. The importance of these findings on the infection susceptibility of patients anesthetized with epidural anesthesia plus epinephrine remains to be investigated.

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RISK OF ABBREVIATING MAJOR CROSSMATCH

The risk of abbreviating the major crossmatch in urgent situations by issuing blood after an "immediate spin" phase was evaluated by a retrospective study of 82,647 crossmatches performed on serum from approximately 13,950 patients. Although the initial screening test for unexpected antibodies for all patients failed to show agglutination or hemolysis of the reagent red blood cells, agglutination was subsequently noted during at least 1 crossmatch performed for 148 of them. Further evaluation of these patients' sera indicated that most positive reactions were due to weakly reactive low-thermal-amplitude antibodies. Eight of the incompatible crossmatches were related to antibodies in the Kell, Kidd, or Rh systems, and a 9th antibody, anti-E, was identified through subsequent evaluation of a cold antibody-induced crossmatch incompatibility. Issuance of blood in urgent situations after an "immediate spin" phase of the crossmatch, for patients whose red blood cells have been typed and whose sera have been screened for unexpected antibodies, has a low level of risk. *(Oberman HA, Barnes BA, Friedman BA: The risk of abbreviating the major crossmatch in urgent or massive transfusion. Transfusion 18:137-141, 1978)*

Racial Mydriatic Response to Belladonna Premedication

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Although racial differences in the response to conjunctivally instilled mydriatics have been recognized for 50 years, no reports have been published on the mydriatic effects of parenterally administered belladonna derivatives. For this reason, atropine sulfate or scopolamine hydrobromide was administered IM, in doses of either 0.4 or 0.8 mg/70 kg, to American white or black volunteers. Pupillary diameter was measured in diffuse natural daylight before and at standard intervals for 4 hours following drug administration.

The lower dose of atropine produced no significant mydriasis in either racial group. Atropine, in a dose of 0.8 mg/70 kg, produced significant mean peak mydriasis of +1.4 mm in the white group, but insignificant pupillary dilation in the black subjects (mean = +0.6 mm). Scopolamine caused significant mydriasis in all groups, regardless of dose or race. Mean peak pupillary dilation in the black subjects was +1.6 mm at the lower dose and +2.2 mm at the higher dose of scopolamine. Compared to black subjects, the relative magnitude of mydriasis in white subjects was 63% and 36% greater at these respective dose levels; these racial differences were not statistically significant.

These results provide evidence that population genetics influence mydriatic responses to belladonna premedication. In addition, scopolamine premedication appears contraindicated in patients with clinical evidence of latent acute-angle glaucoma. In such individuals, parenteral atropine, administered with caution, appears safe in doses of 0.4 mg/70 kg in white patients and in doses up to 0.8 mg/70 kg in black patients.

BELLADONNA premedication is frequently stated to be safe in glaucomatous patients,[1-3] although it is suggested by several authors that caution be exercised in such situations, especially with regard to scopolamine.[4-7] Though this may be true in patients with chronic simple glaucoma (open-angle glaucoma) and in patients with acute closure glaucoma (narrow-angle glaucoma) who are in remission,[8] there is a greater risk of precipitating an acute attack in persons who suffer from undiagnosed angle-closure glaucoma, particularly if one considers that this syndrome occurs in approximately 1 in 4000 persons over 30 years of age in the racially heterogeneous North American population.[9]

Previous studies of the mydriatic effects of belladonna premedicants lack reference to race or eye color. This would appear to limit their applicability in view of the known lack of efficacy in darkly pigmented eyes of

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conjunctivally applied mydriatics such as atropine,[10,11] homatropine,[12] and ephedrine.[12-14]

The present study was designed to assess the pupillary effects of IM administered atropine and scopolamine in white and black American volunteers.

METHODS

This study was approved by the Human and Animal Investigation Committee of the Wayne State University School of Medicine. Written informed consent was obtained from all subjects.

The subjects in the study group were 25 Negro and 25 Caucasian volunteers, ranging in age from 18 to 57 years. Of these subjects, 26 were female and 24 were male, and all were in good health. Iridial pigmentation was not matched in the two racial groups. Individual treatments were assigned randomly and were administered on a double-blind basis. Subjects reclined on a hospital bed for 10 minutes before control measurement of pupillary diameter was made. Fifteen minutes after the control measurement had been recorded, each volunteer received a single IM injection of either isotonic saline, atropine sulfate (0.4 or 0.8 mg/70 kg), or scopolamine hydrobromide (0.4 or 0.8 mg/70 kg).* Pupillary diameter was recorded at 15-minute intervals for 1 hour, at 30-minute intervals during the 2nd and 3rd hours, and at the end of 4 hours. All observations were made in diffuse daylight without artificial illumination.

Transverse pupillary diameters were measured to the nearest millimetre using a standard ophthalmic pupillometer held 3 inches from the left eye of the subject, and are reported as mean ± SE. The data (exclusive of saline responses) were subjected to computer analysis of variance to determine interaction among race, drug, and dose level, and to the Newman-Keuls procedure for ranking means to determine the significance in each treatment group of postinjection pupillary diameters as compared to control pupillary diameter.†

RESULTS

Applying the unpaired Student's *t*-test, no significant difference was found between the mean control pupillary diameter in 25 black and 25 white subjects (3.52 ± 0.87 and 3.36 ± 0.86 mm, respectively). Saline administration did not significantly alter pupillary diameter in either race during the 4 hours of observation, although the 5 white subjects exhibited a slight decrease in mean pupillary diameter, ranging from 0 to 0.4 mm, and the 5 black subjects a slight increase, ranging from 0 to 0.8 mm, during this time.

The effects of atropine administration are listed in table 1. Some degree of mydriasis was seen in 8 out of 10 white volunteers and in 5 out of 10 in the black group. Race thus does have a statistically significant influence upon the response to the drug at both dose levels. Mean peak millimetre change in pupillary diameter following the low dose of atropine was +0.6 mm (range, −1 to +2 mm) in whites, and +1.0 mm (individual range, 0 to +2 mm) in blacks; following the high dose of atropine it was +1.4 mm (range, 0 to +3 mm) in whites, and +0.6 mm (range, 0 to +2 mm) in blacks. The mean mydriatic response was statistically significant only in white subjects receiving

*Coded ampules of injectable drugs and saline were generously supplied by Burroughs Wellcome.

†The authors gratefully acknowledge the statistical consultation of Dr. Glenn Cummings, Department of Physiology, Wayne State University School of Medicine.

TABLE 1
Effects of Atropine on Pupillary Diameter

Race and dose (mg/70 kg) ($n = 5$)	Mean pupillary diameter (mm)									
White, 0.4	3.4	3.4	4.0	4.0	3.8	3.4	3.8	3.6	3.8	3.8
Black, 0.4	3.2	3.4	3.6	4.0	4.0	4.2	4.2	4.2	4.2	3.8
White, 0.8	2.8	3.0	3.2	3.2	4.2*	4.2*	4.2*	4.0*	4.0*	4.0*
Black, 0.8	3.6	3.8	4.0	4.2	4.2	4.2	4.0	4.0	4.0	4.0
Time after injection (min)	−15	15	30	45	60	90	120	150	180	240

*Significantly different from corresponding preinjection (−15 min) control value ($p = 0.05$)

TABLE 2
Effects of Scopolamine on Pupillary Diameter

Race and dose (mg/70 kg) ($n = 5$)	Mean pupillary diameter (mm)									
White, 0.4	3.0	4.2*	4.4*	4.8*	5.4†	5.4*	5.6*	5.6*	5.6*	5.2*
Black, 0.4	3.0	3.0	3.4	3.8	4.2	4.6*	4.4	4.4*	4.0	3.8
White, 0.8	3.6	4.0	5.4†	6.4†	6.4†	6.4†	6.4†	6.6†	6.4†	6.4†
Black, 0.8	3.6	4.4	4.8	5.2*	5.2*	5.8†	5.2†	5.6†	5.6†	5.2*
Time after injection (min)	−15	15	30	45	60	90	120	150	180	240

*Significantly different from corresponding preinjection (−15 min) control value ($p = 0.05$)

†Significantly different from corresponding preinjection (−15 min) control value ($p = 0.01$)

0.8 mg/70 kg atropine. In this group, the onset of significant mydriasis occurred between 45 and 60 minutes and lasted for more than 3 hours. The mean peak mydriasis of 0.6 mm observed both in whites with the low dose of atropine, and in blacks with the high dose, indicates that atropine is twice as potent a mydriatic in whites as in blacks.

Scopolamine produced mydriasis, ranging from +1 to +4 mm in each of the 20 subjects in the study (table 2). Mean mydriatic response was statistically significant in each of the 4 treatment groups. Mean peak change in pupil diameter following the low dose of scopolamine was +2.6 mm (range, +1 to +4 mm) in white, and +1.6 mm (range, +1 to +3 mm) in black subjects. Following the high dose of scopolamine, mean peak change in pupil diameter was +3.0 mm (range, +2 to +4 mm) in white, and +2.2 mm (range, +2 to +3 mm) in black subjects. Although the influence of race upon response at either dose level was of no statistical significance, white subjects exhibited a 63% greater mydriasis at 0.4 mg/70 kg than did black subjects. The time of onset of significant mydriasis occurred within 15 to 30 minutes in the white, compared to 45 to 90 minutes in the black group.

DISCUSSION

No difference in control pupillary diameter was observed in our white and black subjects in diffuse daylight. This is in accord with the observations of Barbee and Smith,[15] who found no significant differences in American Negro and Caucasian pupillary diameter under unspecified lighting conditions, as well as with those of Emiru[12] who studied African Negro and European eyes in natural daylight. Obianwu and Rand[14] found control pupillary diameter in Negroes to be about one-half that in Caucasians. However, these measurements were made under strong artificial illumination and may reflect a stronger miotic reflex in Negro subjects under bright lighting conditions. The similarity of control pupillary diameter in blacks and whites in this study is an aid to the interpretation of our results, inasmuch as the initial pupillary diameter has been reported to significantly correlate with the mydriatic effect of phenylephrine in both a negative[16] and a positive[14] fashion.

Several authors have noted the effect of iridial pigmentation upon the pupillary response to topical mydriatics since Howard and Lee,[17] in 1927, first reported that the Chinese eye was more refractory to ephedrine than the Caucasian eye. Other studies[13-15] have confirmed that increasing pigmentation of the irides progressively impedes ephedrine mydriasis. Conjunctival installation of 4% homatropine was found by Emiru[12] to elicit prompt mydriasis of $>+5.0$ mm in both Caucasians and albino Africans, while the black African eye was only one-half as responsive.

The refractory nature of pigmented irides to mydriatics has been variously attributed to mechanical impedance of drug absorption into the iris,[17] to enhanced tyrosinase activity which reduces the amount of dilatatory adrenergic neurotransmitter in the iris,[18] and to genetically determined adaptation to a bright tropical environment.[14,16]

The present authors are aware of only three studies concerning the mydriatic effects of IM belladonna premedication, none of which notes the racial composition or eye color of the subjects. Leopold and Comroe[4] found that 0.6-mg atropine produced pupillary dilation of 0.5 to 1.5 mm in 3 of 8 sub-

jects, while 0.4- to 0.6-mg scopolamine produced a mydriatic response of 0.5 to 2.0 mm in 7 of 8 subjects. These authors suggested caution in the use of preanesthetic atropine, as well as scopolamine, in glaucomatous patients.

Schwartz et al[8] reported that atropine or scopolamine, in doses of 0.4 to 0.6 mg, caused mydriasis of up to +1.0 mm in 11 of 15 subjects with either angle-closure glaucoma in remission or open-angle glaucoma. They concluded that parenteral belladonna premedication is without danger in such patients. Similar conclusions were reached by Mehra and Chandra,[2] who reported that only 13 of 100 subjects who received 1.12 mg/70 kg atropine IM exhibited mydriasis of up to 2 mm. In this latter study, however, all the subjects were presumably Indians with darkly pigmented irides, which could account for the limited mydriatic response.[14]

The present study confirms the greater mydriatic effect of scopolamine compared to atropine, the overall mean peak increase in pupillary diameter being 2.35 mm and 0.9 mm, respectively. Among the 20 individuals receiving atropine in this study, only 1 white subject exhibited peak mydriasis of >2 mm. Among the subjects given scopolamine, 12 of 20 exhibited peak mydriasis of >2 mm. In addition, 5 of 10 white subjects showed pupillary dilation of +4 mm, while none of the 10 black subjects did so. These results indicate that significant mydriasis is unlikely to be produced by atropine premedication either in white individuals with doses of 0.4 mg/70 kg, or in black individuals with doses of up to 0.8 mg/70 kg. However, scopolamine premedication, even in doses of 0.4 mg/70 kg, produces significant mydriasis in both races. Although the magnitude of pupillary dilation in our white subjects was 63% greater than in our black subjects, this difference was not statistically significant.

The greater potency of scopolamine in this study reflects, in large part, the relative pharmacologic inactivity of the D-hyoscyamine fraction of atropine (DL-hyoscyamine). However, Domino and Corssen have shown that, in equimolar doses, scopolamine displays greater peripheral anticholinergic potency than L-hyoscyamine.[19]

Although precipitation of angle-closure glaucoma by the mydriatic effects of belladonna premedicants is rare, special precaution must be exercised in the case of far-sighted, elderly Caucasian females, a group in which this form of glaucoma occurs most frequently.[7] Such precaution is especially necessary in cases where there is a positive family history of glaucoma, a history of eyeaches and blurred vision developing in darkened surroundings, and where there are objective findings of a shallow anterior chamber, iridial atrophy, unequal pupil size, or irregular pupillary margins.[7]

The results of the present study indicate a difference in mydriatic potency of IM administered atropine and scopolamine and a racial difference in mydriatic response. The results of this study also indicate that scopolamine premedication appears to be contraindicated in patients with clinical evidence of latent acute-angle glaucoma. Parenteral atropine administration appears to be safe in such patients, if employed with caution, in doses of up to 0.4 mg/70 kg in white, and up to 0.8 mg/70 kg in black individuals.

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PENTOBARBITAL THERAPY IN METABOLIC COMA

In severe Reye's syndrome, with nonspecific intensive supportive therapy, the mortality rate approaches 75%. In many instances, death is due to uncontrolled cerebral edema and elevated intracranial pressure (ICP). Pentobarbital therapy, sufficient to maintain a blood barbiturate level between 2.5 mg% and 4.0 mg%, was used to control ICP in 7 patients with metabolic coma complicated by intracranial hypertension (intracranial pressure, 30 mm Hg for 30 min). The nadir of their neurological function was characterized by absent response to deep pain, absent or abnormal oculocephalic responses, bilaterally dilated, unreactive pupils, and markedly irregular or absent respirations. Before barbiturate administration, hyperventilation, steroids, mannitol, and other supportive therapies were begun. After institution of pentobarbital therapy, the daily mannitol dose required to maintain the intracranial pressure below 20 mm Hg was significantly reduced ($p<0.001$), from 3.7 $\pm$ 0.3 to 0.5 $\pm$ 0.2 g/kg/day. All the patients survived, and 6 have no obvious neurological sequelae. Pentobarbital is a useful adjunct for intracranial pressure control in advanced metabolic coma. *(Marshall LF, Shapiro HM, Rauscher A, et al: Pentobarbital therapy for intracranial hypertension in metabolic coma: Reye's syndrome. Crit Care Med 6:1-5, 1978)*

Tracheal Pathology Following Short-Term Intubation with Low-and High-Pressure Endotracheal Tube Cuffs

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Histologic sections of dog tracheas were taken from 20 dogs anesthetized and intubated for 5 to 7 hours with high-pressure, low-volume Shiley or low-pressure, high-volume Lanz endotracheal tubes. Microscopic examination and measurement showed that while the high-pressure, low-volume cuff produced deeper average mucosal erosion, the large-volume, low-pressure cuff resulted in significantly greater lengths of tracheal mucosa-cuff erosion. Maximal depth of penetration through the basement membrane was similar in both groups. Grooves in the mucosa were seen in 50% of the high-volume-cuff trachea sections but none of the low-volume-cuff tracheal sections. These findings demonstrate that low-pressure, high-volume endotracheal tube cuffs produce different but significant tracheal damage after short-term intubation when compared to high-pressure, low-volume cuffs.

Key Words — ANESTHETIC TECHNICS, endotracheal. EQUIPMENT, cuffs, endotracheal. LUNG, trachea.

TRACHEAL erosion following long-term endotracheal or tracheostomy tube intubation has led to the use of high-residual-volume, low-pressure endotracheal tube cuffs in patients in intensive care units as well as during operation. Two recent reports[1,2] demonstrate that the incidence and severity of postoperative sore throat is significantly greater in patients intubated with high-volume, low-pressure endotracheal tube cuffs than those intubated with low-volume, high-pressure cuffs. These studies indicated that strong positive correlation existed between tracheal-cuff contact area and incidence and magnitude of postoperative sore throat. The present investigation was designed to elucidate a possible mechanism for the above findings.

METHODS

Two groups of 10 mongrel dogs (18 to 22 kg in weight) had anesthesia induced with sodium thiopental (10 to 12 mg/kg IV), were paralyzed with succinylcholine (1.5 mg/kg IV) and were atraumatically intubated with unlubricated, sterile, new 8.0-mm-ID polyvinyl chloride Lanz (high-volume, low-pressure) or Shiley (low-volume,

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high-pressure) endotracheal tubes. The cuffs of both types of tubes were inflated to seal with air and maintained at constant pressure via a Moore Nullmatic pressure regulator.* This regulator was powered with a compressed air source and connected to the cuff pilot tube so that constant pressure was maintained at the sealing pressure, preventing changes due to N_2O diffusion. Cuff pressure was continuously monitored with a sphygmomanometer via a 4-way stopcock. Anesthesia was maintained with halothane, 1 to 1.5%, and N_2O, 60%, in O_2.

Following 5 to 7 hours of continuous cuff inflation, the endotracheal tube and trachea were excised together and removed. The boundaries of cuff-tracheal wall contact were marked with suture material and the trachea was sectioned in a cervical to caudal fashion. Wrinkles in the cuff upon its removal from the trachea were noted when present. After fixation of the specimens in 10% formalin, standard hematoxylin and eosin stained slides were prepared. A double-blind protocol was maintained such that the pathologist was unaware of which tube had been used. Following preparation of microscopic slides, the outlines of cuff impingement upon the tracheal specimen were marked and measured with a Scientific Products micrometer. Suture materials in the tracheal specimens were removed and were not present in the microscopic specimens. The cuff outline was then submarked into millimeter divisions and the length (cephalad to caudal) of mucosal erosion measured. Each millimeter of cuff-tracheal area was then examined microscopically, and erosion into the mucosa and/or submucosal connective tissue was measured with a calibrated American Optical Lens. Depending on the length of erosion, the number of measurements of erosion depth varied from 6 to 23 in each trachea examined. The mean depth of erosion in each trachea was determined by averaging all measurements. The mean depth of erosion produced by each type of cuff was calculated by averaging the mean erosion depth of each trachea examined. The site of deepest mucosal erosion was determined and measured with the calibrated ocular. Appearance of grooves through the area of cuff-tracheal contact were noted when present.

Mean intubation time, intracuff pressure, mucosal erosion length, and depth of mucosal erosion were computed. Chi-square and Student's *t*-tests for unpaired data were used to determine statistical significance.

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RESULTS

Intubation time was similar in both groups of dogs but intracuff pressure, as expected, was markedly higher in the high-pressure, low-volume cuffs than in the low-pressure, high-volume cuffs (table). Fifty percent of cuffs removed from dog tracheas intubated with Lanz endotracheal tubes, but none of the cuffs intubated with Shiley tubes, showed evidence of wrinkling. Tracheas intubated with the low-pressure, high-volume cuffs had tracheal mucosa-cuff erosion lengths that were significantly greater than tracheas intubated with high-pressure, low-volume cuffs (table). Average depth of mucosal and submucosal (connective tissue) erosion was significantly greater in low-volume, high-pressure-cuff intubated tracheas but mean maximal depths of penetration through the basement membrance were similar in both groups. Sharply delineated mucosal grooves were seen in 50 percent of high-volume tra-

TABLE

Tracheal Pathology Following Short-Term Intubation (Mean ± SD)

Endotracheal tube cuff	Time (min)	Mean intracuff pressure (mm Hg)	Mean mucosal erosion depth (μ)	Mean mucosal erosion length (mm)	Mean maximal depth of erosion (μ)	Specimens with evidence of wrinkling (%)
Lanz (low-pressure, high-volume)	341 ±50	24* ±4	15.3* ±0.6	20.7* ±6.8	40.0 ±10.2	50†
Shiley (high-pressure, low-volume)	367 ±52	242 ±21	22.9 ±0.4	11.3 ±4.1	42.5 ±9.3	0

*$p<0.001$ using Student's unpaired *t*-test when compared to Shiley tubes

†$p<0.005$ using chi-square test when compared to Shiley tubes

chea sections (the same tracheas that had cuffs with wrinkles) but none of the low-volume-cuff trachea sections.

DISCUSSION

The development of large-volume, low-pressure endotracheal tube cuffs was a direct result of tracheal erosion observed in patients with endotracheal or tracheostomy tubes with high-pressure cuffs kept in place for intervals of several days or longer.[3-11] Recently, these tubes and cuffs have become popular for use in the operating room. Theoretically, if there is less erosion, there should be less morbidity postoperatively and this should be reflected in a reduced incidence and magnitude of sore throat and hoarseness. Clinical studies have shown the opposite result and suggested that the incidence of postoperative sore throat and hoarseness is correlated with length and area of tracheal impingement.[1,2]

The data presented in this study show that there are great differences in the patterns of tracheal mucosa erosion after intubation with large-volume, low-pressure versus low-volume, high-pressure endotracheal tube cuffs. Large-volume, low-pressure cuffs produce less average depth of tracheal mucosa erosion after approximately 6 hours of intubation than low-volume, high-pressure cuffs but the erosion is evidenced over a much larger length of tracheal mucosa.

Interestingly, there was no significant difference in the mean maximal erosion of the tracheal mucosa with the two cuffs studied despite a tenfold difference in intracuff pressures. When grooves were seen microscopically in the tracheal sections of low-pressure cuffs, they frequently were the deepest point of cuff erosion. These grooves were probably the consequence of wrinkling of the cuff as it was inflated. Wrinkling has been previously demonstrated in tracheal simulation models.[1,12] Mucosal grooves were only seen in the large-volume-cuff intubated specimens. Recent work from this laboratory* demonstrates that wrinkling and consequent tracheal mucosal erosion and groove formation occur with most currently available large-volume, low-pressure endotracheal tube cuffs. Together, the greater area of tracheal erosion and evidence of wrinkling and mucosal grooves may account for the higher incidence and magnitude of postoperative sore throat observed with high-volume, low-pressure cuffs.[1,2]

Our findings suggest current low-pressure, high-volume cuffs produce different but significant tracheal damage after short-term intubation when compared to high-pressure, low-volume cuffs. In light of this and previous data[1,2] the need to use large-volume, low-pressure cuffs on endotracheal tubes for surgical procedures less than 6 hours in length appears questionable. Furthermore, the wrinkling of these cuffs produces distinct disadvantages. Perhaps reduction of the excessive amount of cuff fabric, in relationship to the endotracheal tube diameter, would reduce wrinkling. The total surface area of cuff-tracheal impingement should be as small as possible for short-term use.

*Loeser EA, unpublished data

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Interaction of Muscle Relaxants and Local Anesthetics at the Neuromuscular Junction

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The effects on neuromuscular (NM) function of combinations of relaxants (d-tubocurarine, pancuronium, and succinylcholine) and local anesthetics (cocaine, procaine, lidocaine, etidocaine, and a quaternized derivative of procaine, procaine methobromide) were investigated using the rat's phrenic nerve–hemidiaphragm preparation. Combinations of ineffective concentrations of NM blocking agents with ineffective concentrations of local anesthetics caused a greater than 90% NM block. Preliminary administration of ineffective concentrations of local anesthetics significantly ($p<0.001$) decreased the ED50 of NM blocking agents. The administration of ineffective concentrations of NM blocking agents caused a similar decrease of the ED50 of local anesthetics. Concentrations of d-tubocurarine and pancuronium which alone produced partial NM block had additive effects. These findings suggest that the interaction of NM blocking agents and local anesthetics consists of true potentiation caused by the different sites of action of the two types of compounds at the NM junction. The degree of potentiation may be enough to cause clinically significant NM block in patients who at the same time receive high enough doses of both agents. In vitro the NM block caused by the combinations of local anesthetics and NM blocking agents can be reversed by 4-aminopyridine.

Key Words—ANESTHETICS, local, neuromuscular junction. ANESTHETICS, local, interaction with relaxants. NEUROMUSCULAR RELAXANTS, interaction with local anesthetics. INTERACTIONS (DRUG), local anesthetics and relaxants.

It has been known for more than a half century[1,2] that procaine can produce neuromuscular (NM) block and that in vivo it increases the NM responses to both d-tubocurarine chloride (d-Tc) and, under certain conditions, succinylcholine chloride (SCh) in animals[3] and in man.[4] Subsequently several reports were published on the in vivo interactions between procaine and other local anesthetics (eg, lidocaine, mepivacaine, prilocaine, bupivacaine) at the human NM junction.[5-7] In some of these studies apnea was used as the criterion of NM block but there can be little doubt that apnea was significantly contributed to by depression of the respiratory center caused by the large doses of procaine (up to 36 mg/kg) and lidocaine (up to 18 mg/kg) administered to the patients being studied at a time when they were anesthetized with thiopental sodium.[5] Telivuo and Katz,[7] who measured both NM transmission and tidal volume after the administration of considerably smaller doses of local anesthetics (eg,

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3 mg/kg lidocaine, mepivacaine, or prilocaine or 0.75 mg/kg bupivacaine) to patients recovering from alcuronium chloride–induced NM block still found that the depression of tidal volume (by 23.1 to 40 2% of control) was significantly higher than the depression of NM transmission (5.0 to 7.5%).

To eliminate the influence of central respiratory and central and peripheral circulatory effects of local anesthetics on the NM effects of local anesthetics and NM blocking agents, it was decided to investigate the interaction of the NM effects of these agents using an in vitro rat phrenic nerve–hemidiaphragm preparation.[8] The second objective of the study was investigation of the effect of 4-aminopyridine hydrochloride (4-APYR) on the NM block induced by the combination of local anesthetics and NM blocking agents. It was observed earlier that 4 to 8 μg/ml 4-APYR increased twitch tension of the indirectly stimulated phrenic nerve–diaphragm preparation of the rat by about 70% and antagonized the NM block caused by nondepolarizing relaxants, Ca^{++} lack and Mg^{++} excess (Foldes FF et al: Unpublished observations, 1976).

MATERIAL AND METHODS

The experiments were carried out on the phrenic nerve–hemidiaphragm preparation of male Sprague-Dawley rats of 300 to 350 g body weight. The animals were lightly anesthetized with ethyl ether and decapitated, the hemidiaphragms with their corresponding phrenic nerves dissected, and the preparations suspended in organ baths of 60- to 70-ml capacity, in mammalian Krebs' solution. The costal margin of the diaphragm was attached to small hooks protruding from a light metal frame, which in turn was fixed with a strong thread to the bottom of the organ bath. The tendon of the muscle was attached with another thread to a Grass Model FT103 force displacement transducer. The Krebs' solution was aerated with a 95% O_2, 5% CO_2 mixture; its temperature was maintained at 37 C. The pH of the bath was between 7.35 and 7.45.

The diaphragms were indirectly stimulated through their phrenic nerves, placed on platinum electrodes immersed in the bath, with supramaximal stimuli of 0.1 msec duration, at the rate of 0.1 Hz from a Grass Model S48B stimulator. Ten grams of resting tension was applied to the muscles before the start of the experiments. The twitch tension was recorded on a Grass Model 5B polygraph.

The NM blocking agents used were d-Tc, pancuronium bromide, and SCh. The local anesthetics used were cocaine hydrochloride, procaine hydrochloride, lidocaine hydrochloride, etidocaine hydrochloride, and a quaternized derivative of procaine, procaine methobromide.* Procaine methobromide was included in the group of compounds to be studied to obtain more information on the site of the NM effect of local anesthetics. Because its physicochemical characteristics (eg, degree of ionization) are different from those of tertiary local anesthetics, procaine methobromide is less likely to penetrate the nerve and muscle membranes and exerts its pharmacological effects on the extracellular components (eg, outer surface of the postjunctional membrane of the NM junction). The differences in the NM effects of this quaternary compound and its tertiary analog, procaine, should be informative regarding the possible site of action of both compounds (see discussion).

At first the computer derived dose-response regression lines of the NM effects were determined for each compound. The regression lines were linear between 20 and 80% block. ED50 concentrations were individually determined from the regression lines in all experiments, and from these values the mean and the standard error of the mean (SEM) of the ED50 of each compound were calculated. The concentrations of each compound which caused a 90 to 98% NM block (ED90 value) were recorded in every experiment and the means and SEM of the ED90 concentrations were also calculated for each compound. In other experiments the ED50 and ED90 values of the three NM blocking agents were determined after the preliminary addition of 40, 50, 25, 5, or 80 μg/ml cocaine, procaine, lidocaine, etidocaine, or procaine methobromide, respectively. Similarly, the ED50 and ED90 values of the 5 local anesthetics were also determined after the preliminary addition

*Lidocaine hydrochloride (Xylocaine®) and etidocaine hydrochloride (Duranest®) were kindly supplied by Astra Pharmaceutical Products, Inc., Framingham, Massachusetts 01701; tetracaine hydrochloride (Pontocaine®) and bupivacaine hydrochloride (Marcaine®) by Winthrop Laboratories, New York, New York 10016; and procaine methobromide, lidocaine methobromide, and lidocaine ethobromide were synthetized by Professor K. Nador, Chairman of the Department of Chemistry of the Veterinary University of Budapest, Hungary.

of 0.3, 0.9, and 3.0 μg/ml d-Tc, pancuronium, and SCh, respectively. In some experiments, reversal of the NM block caused by the individual compounds and by their various combinations was observed, after washing the preparations with Krebs' solution and adding 4 μg/ml 4-APYR. In other experiments 4-APYR was added first and the Krebs' solution was changed thereafter.

All concentrations referred to are final bath concentrations. The number of experiments is indicated in the tables. The data collected were analyzed for significance with Student's *t*-test.

RESULTS

Combinations of ineffective or marginally effective concentrations of procaine or lidocaine with equally ineffective concentrations of d-Tc or SCh (figure) caused almost complete depression of the indirect twitch tension of the hemidiaphragm preparations. Similar combinations of other local anesthetics (eg, 2-chloroprocaine hydrochloride, tetracaine hydrochloride, bupivacaine hydrochloride, lidocaine methobromide, and lidocaine ethobromide) with these 2 NM blocking agents and also with pancuronium had the same effect on twitch tension. Neostigmine partially reversed the NM block caused by the combination of procaine or lidocaine with d-Tc, but had no antagonistic effect on the NM block induced by combinations of these local anesthetics with SCh (figure). 4-APYR increased twitch tension to above control values after the procaine–d-Tc and lidocaine–d-Tc combinations but only partly antagonized the NM block induced with procaine followed by SCh and had no effect on the block caused by lidocaine followed by SCh.

The addition of 40, 50, 25, 5, or 80 μg/ml cocaine, procaine, lidocaine, etidocaine, or procaine methobromide to the bath significantly ($p<0.001$) decreased both the ED50 (table 1) and ED90 (table 3) concentrations of d-Tc, pancuronium, and SCh. Similarly, the addition of 0.3, 0.9, or 3.0 μg/ml d-Tc, pancuronium, of SCh significantly

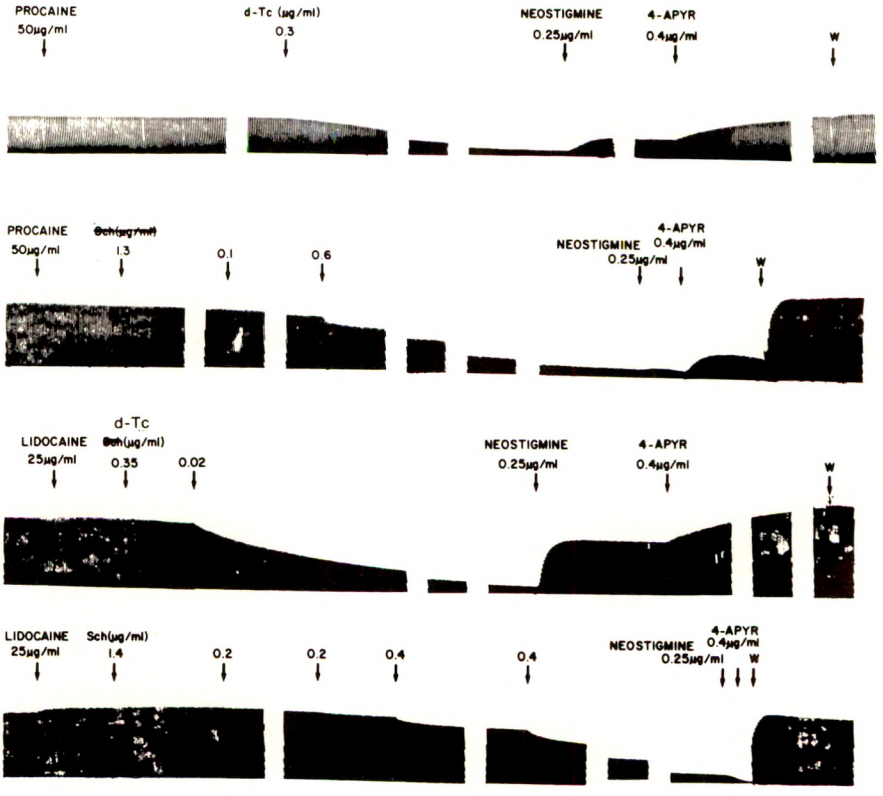


FIGURE. Potentiation of the NM effects of local anesthetics by NM blocking agents. Note that when ineffective concentrations of procaine and lidocaine are combined with ineffective concentrations of d-tubocurarine (d-Tc) or succinylcholine (SCh), they produce about 90% NM blockade. See text for discussion of the antagonistic effect of neostigmine and 4-aminopyridine (4-APYR).

TABLE 1

Influence of Local Anesthetics on Neuromuscular Effects of Relaxants

Neuromuscular blocking agent	ED50 (μg/ml)*					
	Neuromuscular blocking agent alone	Neuromuscular blocking agent preceded by				
		Cocaine (40 μg/ml)	Procaine (50 μg/ml)	Lidocaine (25 μg/ml)	Etidocaine (5 μg/ml)	Procaine-methobromide (80 μg/ml)
d-Tubocurarine	0.48 ± 0.02† (12)‡	0.24 ± 0.03 (4)	0.17 ± 0.00 (4)	0.25 ± 0.01 (4)	0.36 ± 0.04§ (4)	0.11 ± 0.01 (4)
Pancuronium	2.16 ± 0.02 (11)	1.05 ± 0.07 (5)	0.83 ± 0.07 (4)	1.00 ± 0.05 (4)	0.70 ± 0.06 (4)	0.89 ± 0.94 (4)
Succinylcholine	7.28 ± 0.06 (12)	0.95 ± 0.07 (4)	1.02 ± 0.02 (4)	1.12 ± 0.01 (4)	1.89 ± 0.13 (4)	1.67 ± 0.12 (4)

†Mean ± SEM

‡Number of experiments

*In the presence of local anesthetics, the ED50's of neuromuscular blocking agents are significantly ($p<0.001$) different from their control values

§This value only significant at the $p<0.05$ level

($p<0.001$) decreased the ED50 concentrations of all local anesthetics (table 2).

After establishment of a 92 to 98% NM block with combinations of NM blocking agents and local anesthetics, independently from the sequence of their addition to the bath, washout with Krebs' solution, with few exceptions, did not return twitch tensions to levels >50% of control. The addition of 4 μg/ml 4-APYR after or before washout, however, increased twitch tensions to or above control values (table 3). There were only 2 exceptions: With the SCh-cocaine and SCh-procaine sequences, twitch tensions returned to 65.9 ± 0.6 and 80.8 ± 1.4% of control, respectively. When the bathing fluid was replaced by drug-free Krebs' solution after the addition of 4-APYR, twitch tensions invariably remained above control values.

DISCUSSION

The present findings indicate that NM blocking agents and local anesthetics significantly increase the NM blocking effects of each other. It is conceivable that this represents true potentiation, since the combined NM effects of the 2 types of compounds are greater than what could be excepted from summation of the effects of the individual compounds. In contrast, the combined NM effect of d-Tc and pancuronium was found to be very similar to that of equivalent concentrations of either of the 2 relaxants. Thus, for example, 0.3 μg/ml of d-Tc together with 1.2 μg/ml pancuronium produced about the same degree of NM block (56%) as 0.6 μg/ml d-Tc (48%) or 2.4 μg/ml pancuronium (48%). Consideration of the mechanism of the NM effects of local anesthetics facilitates understanding of the reasons for this potentiation.

Local anesthetics theoretically may interfere with NM transmission (1) by blocking conduction within the terminal motor nerve fibers, which lose their myelin sheath as they approach the myoneural junction; (2) by inhibiting the synthesis of acetylcholine (ACh); (3) by decreasing the ACh content of the quanta or the number of quanta released at rest or during nerve stimulation; (4) by interfering with the adsorbtion of ACh to its receptor sites on the postjunctional membrane; (5) by altering the process of endplate depolarization-repolarization sequence after formation of the ACh-receptor couples; or (6) by interfering with the contraction of the muscle fibers.

TABLE 2
Influence on Neuromuscular Blocking Agents on Neuromuscular Effects of Local Anesthetics

Local anesthetic	ED50 (μg/ml)*			
		Local anesthetic agent preceded by		
	Local anesthetic alone	d-Tubocurarine (0.3 μg/ml)	Pancuronium (0.9 μg/ml)	Succinylcholine (0.3 μg/ml)
Cocaine	81.0 ± 4.70† (4)‡	32.0 ± 2.70 (4)	40.4 ± 1.04 (4)	8.2 ± 0.79 (4)
Procaine	108.4 ± 4.40 (6)	20.7 ± 0.67 (4)	26.2 ± 1.14 (4)	20.0 ± 0.62 (4)
Lidocaine	62.3 ± 2.00 (6)	12.6 ± 0.28 (4)	18.9 ± 0.65 (4)	20.8 ± 1.38 (4)
Etidocaine	9.5 ± 0.30 (4)	4.1 ± 0.16 (4)	4.0 ± 0.34 (4)	2.8 ± 0.27 (4)
Procaine-methobromide	182.0 ± 1.50 (4)	50.2 ± 1.83 (4)	86.4 ± 1.93 (4)	19.3 ± 2.68 (4)

*In the presence of neuromuscular blocking agents, the ED50's of local anesthetics are significantly ($p<0.001$) different from their control values.
Meaning of other symbols as in Table 1

Considerable experimental evidence indicates that local anesthetics block conduction in nerve fibers by blocking the Na^+ channels,[9,10] and that smaller concentrations are required for this in small-diameter[11] nonmyelinated and myelinated fibers[12] than in larger myelinated fibers. Concentrations of local anesthetics (eg, 0.5 Mm lidocaine) necessary for this effect were of the same magnitude as those which depressed the indirectly stimulated twitch tension in this study.

There is no indication that local anesthetics inhibit ACh synthesis, but it has been reported[13] that low concentrations of local anesthetics reduce the amplitude, but not the frequency, of miniature endplate potentials (MEPP). It is generally accepted that the amplitude of MEPP depends on ACh content of quanta and their frequency on the number of quanta released per minute in the nonstimulated (resting) nerve. Thus, the influence of local anesthetics on these parameters indicates that they do not interfere with the number of quanta released but they either decrease the ACh content of the quanta or decrease the sensitivity of the postjunctional membrane to ACh. Local anesthetics decrease ACh release during nerve stimulation in the rat's phrenic nerve diaphragm preparation.[14,15] Local anesthetics inhibit the increase of the twitch tension caused by anticholinesterases both in vivo in cats[16,17] and rats[18] and in vitro in rats.[11] This effect of local anesthetics may be due to decreased ACh release, interference with the effects of ACh on the postjunctional membrane, or both. The prolongation of the absolute refractory period[19] and depression of posttetanic repetitive activity[20] caused by local anesthetics may also be attributed to their presynaptic effect.

There is ample evidence for the postjunctional effect of local anesthetics. Thus, procaine inhibits ACh contracture of frog muscles,[21,22] and it has been suggested that local anesthetics inhibit the adsorbtion of ACh to its receptors.[13,21,22,23] Recently, however, it has been shown that local anesthetics do not competitively inhibit the adsorption of ACh to its receptors but that they instead interfere with another step of the transmission process.[24] It is probable that the postjunctional action of local anesthetics is caused by the blockage of the Na^+ channels[25] (eg, with procaine) or both the Na^+ and K^+ channels (eg, with lidocaine[26]).

Finally, it has been reported that procaine inhibits release of Ca^{++} from sarcoplasmic reticulum and displaces Ca^{++} from the sarcolemma.[27] Both of these factors may inhibit formation of the contractile actomyosin complex of the muscle fibers and decrease twitch tension during direct stimulation. In agreement with this, local anesthetics, but not their quaternary derivatives, in higher concentrations than those necessary for the inhibition of the twitch tension during indirect stimulation (Rao DBS, Foldes FF: Unpublished observations) also depress the twitch tension of the directly stimulated rat phren-

TABLE 3

Reversal of Neuromuscular Block, Caused by Muscle Relaxants Alone or Preceded by Local Anesthetics, by Washout and 4-Aminopyridine

a. c-Tubocurarine

Local anesthetics			Twitch tension (% of control) after			
Agent	Concentration (μg/ml)	d-Tubocurarine concentration (μg/ml)*	Washout	Washout → 4-APYR†	4-APYR	4-APYR → Washout
None	...	0.92 ± 0.04†	102.3 ± 1.7	169.4 ± 17.4	154.3 ± 10.0	153.6 ± 9.6
Cocaine	40	0.39 ± 0.01	79.6 ± 2.4	139.7 ± 3.5	109.0 ± 5.0	120.6 ± 1.7
Procaine	50	0.29 ± 0.01	90.9 ± 8.1	113.9 ± 3.9	108.3 ± 4.4	113.0 ± 1.4
Lidocaine	25	0.34 ± 0.01	74.1 ± 2.2	122.2 ± 3.0	105.8 ± 4.1	107.7 ± 5.5
Etidocaine	5	0.62 ± 0.01	70.8 ± 4.8	117.5 ± 5.3	103.0 ± 0.7	107.0 ± 3.5
Procaine-methobromide	80	0.14 ± 0.01	79.5 ± 2.3	110.8 ± 0.9	103.0 ± 0.7	116.0 ± 1.2

*Concentrations of d-Tc which caused a >90% block alone or together with the concentrations of local anesthetics indicated. The concentrations of d-Tc which produced NM block of similar intensity were significantly ($p<0.001$) lower in the presence of local anesthetics.
‡Means ± SEM of 4 experiments
†4 μg/ml

b. Pancuronium

Local anesthetics		Pancuronium	Twitch tension (% of control) after			
Agent	Concentration (μg/ml)	concentration (μg/ml)*	Washout	Washout → 4-APYR†	4-APYR	4-APYR → Washout
None	...	3.27 ± 0.09†	99.4 ± 2.7	141.8 ± 9.6	150.1 ± 9.7	130.9 ± 13.5
Cocaine	...	1.42 ± 0.03	78.7 ± 0.7	144.2 ± 2.6	115.5 ± 2.0	115.5 ± 2.0
Procaine	...	1.21 ± 0.04	64.0 ± 0.1	120.2 ± 0.3	102.5 ± 0.2	107.6 ± 3.0
Lidocaine	...	1.29 ± 0.05	69.0 ± 0.4	133.7 ± 15.1	113.7 ± 0.1	126.3 ± 7.9
Etidocaine	...	0.70 ± 0.06	75.0 ± 4.2	140.2 ± 12.2	114.4 ± 1.1	115.7 ± 4.9
Procaine-methobromide	...	0.97 ± 0.03	96.2 ± 0.7	139.1 ± 4.6	101.0 ± 0.7	114.8 ± 7.6

c. Succinylcholine

Local anesthetics		Succinylcholine	Twitch tension (% of control) after			
Agent	Concentration (μg/ml)	concentration (μg/ml)*	Washout	Washout → 4-APYR†	4-APYR	4-APYR → Washout
None	...	10.08 ± 0.36†	98.8 ± 2.6	136.3 ± 8.0	42.7 ± 5.5	127.4 ± 3.4
Cocaine	40	1.12 ± 0.01	81.2 ± 1.6	146.7 ± 2.3	110.0 ± 5.7	130.5 ± 8.1
Procaine	50	1.32 ± 0.01	67.5 ± 1.1	124.4 ± 3.6	108.4 ± 1.5	121.2 ± 5.7
Lidocaine	25	1.52 ± 0.03	68.7 ± 6.1	125.6 ± 1.8	106.6 ± 1.0	.....
Etidocaine	5	2.78 ± 0.03	76.0 ± 4.1	132.0 ± 5.0	112.6 ± 5.7	114.0 ± 6.7
Procaine-methobromide	80	2.03 ± 0.05	88.1 ± 2.7	123.2 ± 2.2	112.0 ± 3.5	121.6 ± 2.6

ic nerve–diaphragm preparation. This difference in the effects of the tertiary local anesthetics and their quaternary derivatives is probably due to the circumstance that the latter compounds are more strongly ionized and therefore do not penetrate into the sarcoplasmic reticulum and do not interfere with the role of Ca^{++} in muscle contraction.

In view of the fact that local anesthetics inhibit conduction in motor nerve fibers, decrease the amount of ACh released by the

nerve impulse, and interfere with the depolarization of the postjunctional membrane, it is not surprising that they potentiate the effects of NM blocking agents which act by competitive inhibition of the adsorption of ACh to the cholinergic receptors.

It is of interest that whereas 4-APYR only antagonized the NM block caused by cocaine, procaine, 2-chlorprocaine, and the quaternary derivatives of procaine and lidocaine(eg, procaine methobromide, lidocaine-methobromide, -ethobromide) but not those of tetracaine and the tertiary-amide-type local anesthetics (Rao DBS, Foldes FF: Unpublished observations), 4-APYR is an effective antagonist of the NM block caused by combinations of NM blocking agents with all local anesthetics.

It is possible that the differences in the antagonistic effects of 4-APYR on the NM block caused by different local anesthetics is due to the circumstance that, depending on their physiochemical characteristics, they block Na^+ channels at different sites[28] or that some (eg, lidocaine) also block K^+ channels.[26] The effect of 4-APYR is attributed to the selective blockade of the K^+ channels,[29] which results in the prolonged opening of the Na^+ channels. Since the influx of Ca^{++} into its sites of action occurs in part through the Na^+ channels,[30,31] it may be that 4-APYR is not effective when both Na^+ and the K^+ channels are already blocked by an agent such as lidocaine. Under these circumstances the Na^+ channels may remain closed, and since local anesthetics can dissociate from open but not from closed channels,[28] 4-APYR will not be an effective antagonist. The site of binding (eg, outer opening, passage, or inner opening) to the Na^+ channel may also influence the dissociation of the local anesthetic from its binding sites and influence the efficacy of 4-APYR.

The situation is different, however, when NM block is produced not by high concentrations of local anesthetics, but by the combination of lower concentrations of local anesthetics and low concentrations of NM blocking agents. Under these circumstances 4-APYR, independent from the combination of local anesthetic and NM blocking agent used, is an effective antagonist of the NM block (see table 3).

The concentrations of local anesthetics and NM blocking agents which together caused significant NM block in the present study are of the same order of magnitude that may be present under clinical circumstances. Thus, for example, Matteo et al[32] reported that at the time of apparently complete clinical recovery of NM activity the serum concentration of d-Tc was 0.20 ± 0.13 μg/ml. This is not significantly different from the 0.34 ± 0.01 μg/ml concentration of d-Tc which in combination with 25 μg/ml lidocaine produced a 90% NM block in this study. Plasma lidocaine levels of this magnitude may be approximated in patients with poor circulation, who for the treatment of arrhythmia receive a 100-mg bolus of lidocaine followed by the continuous IV infusion of this agent at the rate of 3 to 4 mg/min.

For this reason care should be exercised when lidocaine is administered IV to surgical patients for the treatment of cardiac arrhythmias when they concomitantly have received NM blocking agents. Such concern is especially justified in poor-risk patients with fluid and electrolyte imbalance who also received antibiotics with NM activity during and after surgery. Under these circumstances the potentiation of the NM effects of local anesthetics and NM blocking agents may cause prolonged apnea, requiring artificial ventilation.

In vivo animal experiments in progress indicate that if and when available for clinical use, 4-APYR promises to be the antagonist of choice for the reversal of this type of NM block.

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Clinical Reports

Pseudohypertension Due to Mönckeberg's Arteriosclerosis

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COMPARISONS of indirect and direct methods of measuring arterial blood pressure have documented frequent discrepancies between indirect and direct readings. Even when a proper-sized cuff and an appropriate rate of deflation of the cuff are used, indirect methods of measuring systolic blood pressure usually yield a value of varying degrees less than true systolic pressure.[1,2] However, because an indirect pressure measurement depends on obliteration of the arterial lumen by cuff-induced lateral arterial wall pressure, arteriosclerosis severe enough to resist compression of the lumen by the cuff theoretically should produce a discrepancy between indirect and direct methods opposite to that usually observed. The following case report documents such a situation in which a falsely elevated indirect arterial pressure determination led to the erroneous diagnosis of an acute hypertensive crisis.

REPORT OF A CASE

An 81-year-old man was transferred to our hospital after he developed signs of gram-negative sepsis following an unsuccessful attempt to reinsert an indwelling urinary catheter. In addition to a history of bladder carcinoma, the patient had an 8-year history of hypertension, for which he had received numerous antihypertensive medications. Previous in-hospital evaluations had revealed maximum indirect blood pressure determinations of 170-190/90-110 torr, a calcified aortic knob, and calcifications of the iliac vessels. The clinical impression was hypertension due to arteriosclerotic cardiovascular disease and renal dysfunction.

On admission, physical examination revealed a disoriented man with a rectal temperature of 40 C and an inaudible blood pressure. Although peripheral pulses were weak, palpation of the blood pressure produced systolic values between 200 and 290 torr. Further examination revealed a grade II/VI systolic ejection murmur along the left sternal border, bilateral basilar rales, the liver palpable 3 cm below the costal margin, grade III funduscopic hypertensive changes, and purulent drainage from the urethra. Pertinent laboratory data included the following: blood urea nitrogen 55 mg/dl, creatinine 4.2 mg/dl, sodium 140 mEq/L, potassium 2.3 mEq/L, bicarbonate 17 mEq/L, chloride 100 mEq/L, Pao_2 60 torr, $Paco_2$ 31 torr, pH 7.43, hematocrit 41.3, white blood cell count 24,800/cu mm. The ECG showed a prolonged P-R segment, left anterior hemiblock, and occasional premature atrial beats. Chest roentgenogram revealed cardiomegaly and a tortuous aorta.

Because of the tentative diagnoses of gram-negative sepsis and hypertensive cardiovascular disease, the patient was treated initially with gentamicin, cefazolin, furosemide, and methyldopa. A subsequent IV pyelogram revealed no left renal function, delayed function of the right kidney, a staghorn calculus in the right intrarenal system,

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and partial obstruction at the level of the right ureterovesical junction with proximal hydronephrosis. Cystoscopy under local anesthesia also showed a small, contracted bladder with an obstruction of the right ureter at the ureterovesical junction. In an attempt to bypass the obstruction, a ureteral catheter was passed and left in place.

After a number of days of conservative management without improvement, the patient was brought to the operating room for the formation of a cutaneous ureterostomy. Upon attempting to establish baseline vital signs, the anesthesiologist was unable to auscultate the blood pressure in any extremity. Determination of the blood pressure by palpation was difficult, but systolic values between 250 and 280 torr were obtained in the left arm; a palpable pressure could not be felt in the other extremities. Also, the pressure could not be determined in any of the extremities with the use of an Infrasonde instrument. However, when a Doppler probe was positioned over the left radial artery, the systolic pressure was determined to be 220 torr. Suspicious that the pressure reading was artificially elevated, we inserted a 20-gauge catheter into the left radial artery. Direct blood pressure values (via a transducer calibrated against a mercury manometer) immediately after insertion ranged from 130-140/80-90 torr, while values obtained simultaneously by palpation and Doppler methods were in excess of 200 torr. Evidence that a noncompliant arterial wall produced these discrepancies was obtained when inflation of an arm cuff proximal to the arterial catheter failed to obliterate the direct arterial pulse trace until a cuff pressure of 280 torr was reached. These discrepancies between indirect and direct readings continued to be observed until the catheter was removed. Subsequent roentgenographic examination of the extremities revealed calcified vessels.

DISCUSSION

Mönckeberg's medial calcific sclerosis is characterized by ringlike calcifications within the media of small- to medium-sized arteries.[3] Occasionally, the patchy deposits within the media coalesce to create a layer of calcification so that the vessel resembles a rigid calcific tube. Because the calcium deposits do not encroach on the vascular lumen, the lesions are usually of little clinical importance. However, when the calcifications are severe enough to resist obliteration of the lumen by sphygmomanometer cuff inflation, falsely elevated indirect blood pressure readings may be recorded.[4,5]

Although indirect methods of measuring systolic blood pressure usually underestimate true systolic pressure and although this discrepancy is even greater in the hypertensive patient,[1,2] pseudohypertension due to severe Mönckeberg's arteriosclerosis is a predictable physiological exception to these observations. Apparently because the disease process does not involve the brachial artery as severely as other peripheral arteries,[3] pseudohypertension has not been commonly reported. Suspicion that one is dealing with such a patient should always arise when the blood pressure is found to be markedly elevated in a patient whose clinical state does not appear to reflect the severity of the pressure elevation. In such a situation, roentgenographic demonstration of calcified arteries will confirm the diagnosis.

In the patient described here, all indirect technics used to measure systolic blood pressure were markedly inaccurate. Although it has been suggested that the Infrasonde technic might be more reliable in situations like the one reported here,[5] this was not the case. No differences in sensitivity were noted among indirect technics.

In summary, this case of pseudohypertension due to Mönckeberg's arteriosclerosis demonstrates that the commonly used indirect methods of measuring blood pressure can be very misleading. Severe Mönckeberg's arteriosclerosis is one disease process in which the indirect methods of measuring arterial pressure do not underestimate but indeed overestimate true systolic pressure.

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Deglutition of an Endotracheal Tube: Case Report

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SUCTIONING the trachea of a newborn through an endotracheal tube when pharyngeal meconium is presumed to be present at birth is a common procedure.[1] This report describes a newborn who actively swallowed an endotracheal tube when the tube was disconnected from its adapter connection during attempted tracheal intubation.

CASE REPORT

A 3480-gram term infant delivered vaginally from a 20-year-old primigravida whose labor and delivery were complicated only by meconium staining of the amniotic fluid at the time the membranes ruptured 4 hours prior to delivery. Immediately following delivery, laryngoscopy revealed meconium at the level of the vocal cords. As a 3.5-mm ID endotracheal tube was placed in the infant's hypopharynx in preparation for intubation and suctioning, the plastic adapter connection by which the tube was being grasped became dislodged from the tube, and the tube disappeared through the actively, rapidly contracting esophageal opening. The patient was then tracheally intubated, suctioned, and extubated with a second tube.

The proximal end of the esophageal tube could not be visualized by direct laryngoscopy. A chest x-ray (figure) revealed the tube to be lodged beneath the cricopharyngeal sphincter and extended down the esophagus into the antrum of the stomach. The infant was in no respiratory distress and handled oral secretions without difficulty. The infant was brought to the operating room, tracheally reintubated while awake and then anesthetized with halothane in air and O_2. Through the use of a rigid esophagoscope, the swallowed tube was easily visualized and removed. No laryngeal or esophageal abnormalities were noted. The patient was discharged three days later following an uneventful postoperative course.

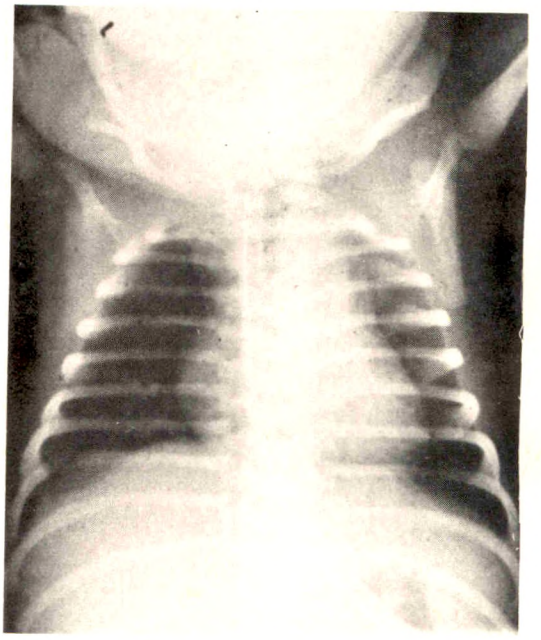


FIGURE. Esophageal location of endotracheal tube

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DISCUSSION

There are numerous complications of tracheal intubation in children,[2,3] Swallowing an endotracheal tube has had previous unreferenced mention as a possible complication,[2] but so far as we are aware this is the first documented case. Most pediatric endotracheal tubes are supplied with the tube and connector either loosely attached or separate. This case demonstrates the importance of assuring that the plastic connector is securely attached to the tube prior to any attempt at tracheal intubation. As a further safeguard, the tube rather than the connector should be held between the fingers. In this case, failure to follow these simple precautions exposed this infant to the hazards of anesthesia and esophagoscopy.

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A Simple Technic for Block of the Spinal Accessory Nerve

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SPINAL accessory nerve block is infrequently used, not only because the nerve has only motor functions but also because previously described technics for blocking it are technically difficult and may be associated with a relatively high incidence of undesirable side effects.

The spinal accessory nerve is made up of a cranial accessory root and a spinal root.[1] Fibers which form the spinal root arise from the spinal nucleus, an elongated column of gray matter situated in the lateral part of the anterior gray column of the spinal cord which extends downward as far as the 5th cervical segment. The roots pass through the lateral white column of the spinal cord and, after emerging between the ventral and dorsal nerve roots of the upper cervical nerves, unite to form a trunk. This ascends into the skull through the foramen magnum and then passes toward the jugular foramen to join the cranial root which arises from the medulla below the roots of the vagus. Shortly after the combined nerve emerges from the jugular foramen, the cranial root separates from the spinal root, joins the vagus, and is distributed peripherally as the accessory part of the nerve along with the branches of the vagus.

After the spinal root separates from the cranial root it crosses the transverse process of the atlas, and, passing medial to the styloid process, reaches the deep surface of the sternocleidomastoid muscle, which it supplies with its motor innervation. The spinal root then emerges from the sternocleidomastoid muscle above the middle of the posterior border of the muscle, and crossing the posterior triangle of the neck, enters the anterior border of the trapezius muscle about 5 cm above the clavicle to supply the trapezius with its motor innervation.

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One of the current technics[2] for blocking both roots of the spinal accessory nerve is designed to produce a block at the level of the 2nd cervical transverse process, underneath the sternocleidomastoid muscle, using a 5-cm needle and 10 ml of local anesthetic. When we utilized this technic, we found it to be unpredictable in blocking the accessory portion of the nerve and frequently associated with hoarseness due to simultaneous block of the vagus as well as with development of a Horner's syndrome due to block of the sympathetic chain. If attempts are made to avoid these complications by blocking the nerve at the jugular foramen, the 9th and 10th cranial nerves are also blocked. On the other hand, if the nerve is blocked at the posterior border of the sternocleidomastoid muscle, only the trapezius muscle is denervated because the nerve has already innervated the sternocleidomastoid before emerging from this muscle. When we reviewed the anatomy, it occurred to us that a simple IM injection into the sternocleidomastoid muscle would produce complete block of the spinal portion of the spinal accessory nerve.

METHODS

The spinal portion of the spinal accessory nerve was blocked in 128 patients who were undergoing neck and shoulder operations under interscalene cervical plexus block, who were being treated in the pain clinic for acute or chronic torticollis, or who were being treated for shoulder and neck pain. Some of the patients received a series of blocks to facilitate physical therapy.

Our method consisted of blocking the nerve in the substance of the sternocleidomastoid muscle (figure). The patient, in the supine position, was asked to elevate his head to allow identification of the posterior border of the sternocleidomastoid muscle. A 23-gauge, 2.5-cm needle was then introduced 2 cm below the tip of the mastoid process and advanced into the belly of the sternocleidomastoid muscle, where the local anesthetic solution was injected.

This technic was used in 14 patients with acute torticollis, in 23 with chronic torticollis, and in 71 with neck and shoulder pain.

In an additional 20 patients the block was performed after completion of an interscalene cervical plexus block, the needle being withdrawn into the subcutaneous tissue and then inserted into the substance of the sternocleidomastoid muscle through its posterior border.

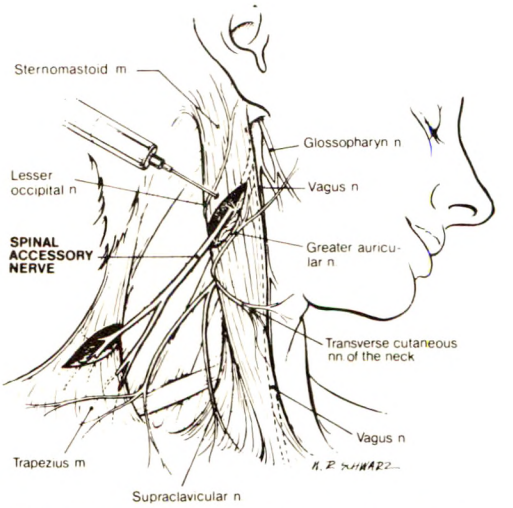


FIGURE. Anatomy and the technic of blocking the spinal accessory nerve in the substance of the sternocleidomastoid muscle

Effects of the block were evaluated by asking the patient to turn his head to the side opposite to that of the muscle being tested in order to contract each sternocleidomastoid muscle, strength of the contraction then being compared on the blocked and unblocked sides. Relaxation of the trapezius muscle was evaluated by asking the patient to shrug his shoulders against resistance to compare motor function of the trapezius muscles.

The volume of local anesthetic injected varied. Ten millilitres were used in 20 patients, 8 ml in 20 patients, 5 ml in 68 patients, 4 ml in 10 patients, and 3 ml in 10 patients.

Local anesthetic agents used included mepivacaine, 2% in 10 patients and 1% in 30 patients; bupivacaine, 0.75% in 10 patients and 0.5% in 73 patients; and chloroprocaine, 2% in 10 patients and 1% in 30 patients. The duration of the block was not evaluated.

RESULTS

Relaxation of the sternocleidomastoid and trapezius muscles was achieved in all but 4 patients. In 2 of these, less than 5 ml of local anesthetic were used. In the other 2, 5 ml were used. When 8 ml or 10 ml were used, there were no failures.

Electromyography in 3 patients confirmed

denervation of the sternocleidomastoid and trapezius muscles.

All patients had slight difficulty in turning the head to the opposite side and in elevating the arm above 90° following the block. Hypesthesia behind the ear due to the block of the lesser occipital nerve was observed in 70 patients.

DISCUSSION

Spinal accessory nerve block provided a better surgical field due to the relaxation of the sternocleidomastoid muscle. It increased the patient comfort due to the decreased need for retraction and decreased "pull" when the head was turned to one side for prolonged periods.

In the pain clinic, block of the spinal accessory nerve relaxed the sternocleidomastoid and trapezius completely, thus facilitating physical therapy in patients with torticollis or neck and shoulder pain.

Even though the spinal portion of the spinal accessory nerve is a motor nerve, relaxation of the sternocleidomastoid and trapezius muscles produced by blocking it often eliminates referred pain originating from these muscles.[3] The sternocleidomastoid and trapezius muscles are involved in many myofascial pain syndromes;[3] relaxation of these muscles is often useful for interrupting the cycle of pain–spasm–pain.

In 2 patients this block was used to predict the effectiveness of surgical section of the sternocleidomastoid or spinal accessory nerve.

Side effects related to the block—ie, difficulty in turning the head due to sternocleidomastoid muscle weakness and difficulty in abducting the shoulder above 90° because of the incomplete upward rotation of the scapula due to the weakness of the trapezius—were inconsequential.

Lesser occipital nerve block with numbness behind the ear was transient lasting only as long as the duration of local anesthetic effect.

Five millilitres is probably the optimal volume. When smaller volumes are used, failure rate increases to 10% from 3%.

It is possible that injection of local anesthetic into a muscle can produce relaxation. When 5 ml of a local anesthetic solution is injected into the sternocleidomastoid muscle below the level of the exit of the accessory nerve, only a localized relaxation of the muscle is produced. Since we obtain complete denervation of both the sternocleidomastoid and trapezius muscles, we are certain that we are, in fact, blocking the spinal accessory nerve.

Because of virtual absence of serious complications and the simplicity of the technic, accessory nerve block by the method we have described can be utilized with benefit in conjunction with other regional anesthetic technics in the neck for surgical as well as for diagnostic and therapeutic purposes.

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Hyperbaric Bupivacaine Peridural Anesthesia in Obstetrics

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THE skillful use of epidural anesthesia in obstetrics has been shown to be of great benefit to both mother and baby. With the introduction of the new longer acting local anesthetics such as bupivacaine these technics have become even more popular. This method of conduction anesthesia properly performed allows the mother to remain comfortable throughout her labor and delivery without the use of drugs having an adverse effect on the newborn.[1]

During the institution of an epidural anesthetic, unintentional dural puncture can

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occur, and in one series of 43,152 cases is reported to have an incidence of 2.5%. This event will usually be recognized by aspiration tests, but unexpected subarachnoid injection can occur. The incidence of unrecognized dural puncture with subsequent subarachnoid injection and total spinal is about 0.2%.[2]

To minimize the effects of such an occurrence we have made our solution of bupivacaine hyperbaric by the addition of 10% dextrose. The specific gravity of the mixture of 30 ml of 0.5% bupivacaine without epinephrine and 15 ml of 10% dextrose is 1.016. Since cerebrospinal fluid has a specific gravity of 1.000 to 1.010, the resulting solution is, as desired, hyperbaric.[3] Should a subarachnoid injection unintentionally occur with the test dose, the resulting blockade would be similar to a saddle block rather than a high or total spinal anesthetic.

The resultant concentration of bupivacaine in this hyperbaric mixture is 0.33%, which provides an excellent sensory blockade while usually sparing motor function, thus allowing the mother to assist in her delivery by bearing down at the appropriate times.

We have employed this technic in a series of 218 vaginal deliveries with very satisfactory results. These epidural anesthetics were usually administered by residents from the Department of Anesthesiology, or from the Department of Obstetrics and Gynecology rotating through the anesthesia program. In this series, unintentional subarachnoid puncture occurred 7 times. In one of these, subarachnoid injection of the local anesthetic resulted. Initially, aspiration through the needle failed to reveal any evidence of cerebrospinal fluid, and a 2-ml test dose plus 5 ml more of 0.33% bupivacaine were injected. At this time, repeat aspiration plus the rapid onset of lower extremity sensory and motor block indicated that subarachnoid injection had occurred. The needle was withdrawn slightly, and the catheter inserted. The patient was placed in the left lateral position (we usually perform our epidurals in the sitting position). The blood pressure was taken and found to be unchanged (500 ml of 5% dextrose in Ringer's lactate had been previously administered). Aspiration through the catheter was negative for cerebrospinal fluid and blood. The muscle block was more profound than usual, but no problems were seen in control of blood pressure and fetal heart rate remained unchanged. Uterine contractions continued uninterrupted.

It was our opinion that only a small portion of the total 7 ml injected went into the subarachnoid space. We base this on the fact that the motor block only involved the lower extremities, and the sensory level was not above the 10th thoracic dermatome and only lasted for 2 hours. At the time of the 2nd injection, aspiration through the catheter was negative for cerebrospinal fluid. Eight millilitres of anesthetic solution were injected into the peridural space with the sensory level again being approximately the 10th thoracic dermatome. There was not an unusual amount of motor block.

At delivery the anesthesia was satisfactory. The baby's Apgar score was 8 and 9 at 1 and 5 minutes, respectively. The patient's postpartum course was uneventful and without postspinal headache, even though the needle used was an 18-gauge Tuohy.

In these 218 patients no problems have been seen relating to the use of dextrose in the epidural solution. The onset and duration of action was well within the times given for the plain solutions.[4] The quality of blockade has also been similar to that reported by other investigators.[5]

Since A. E. Barker[6] published his results in 1907 on the use of glucose in hyperbaric solutions for spinals, glucose has been widely used in spinal anesthesia to control anesthetic level. We believe the extension of this principle to peridural blockade has resulted in an increased margin of safety should unintentional subarachnoid injection occur.

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TOXICITY OF INHALATION ANESTHETICS

To the Editor:

"Who dares to say that he alone has found the truth?"

H. W. Longfellow

The lighted lamp of Diogenes searching in bright sunlight for an honest man illustrates the plight of the scientist searching for truth but blinded by the surrounding brightness. In a practical sense, most helpful in maintaining perspective is the use of a thoughtful and constructive critique provided by knowledgeable colleagues. Unfortunately, an overzealous attack may prove more destructive than enlightening.

To my mind, the review by L. L. Ferstandig[1] appearing in a recent issue of this journal is of the latter type and hence has lost its chance to provide a useful critique of health hazards possibly associated with trace anesthetic gases. Most unfortunate is the fact that with 126 cited references, only a few readers will have the opportunity to search out the required information to separate objective fact from strong personal opinion.

In the decade since Dr. Vaisman[2] first reported her study demonstrating increased hazards among Russian anesthetists, 19 epidemiologic studies in 8 countries have, with few exceptions, provided support to this scientifically naive, but very important, first publication. It is readily acknowledged that many problems are involved in the conduct of epidemiologic research, especially when dependent upon data obtained retrospectively. On balance, however, the information generated from 2 comprehensive surveys which examined all personnel exposed to operating rooms in the United States and all anesthetists in the United Kingdom has by its internal consistency[3] provided meaningful and useful data. In acknowledgment, the governments of Sweden, Denmark, and England have chosen to adopt official regulations to control occupational exposure to anesthetic gases. Our own government, through the NIOSH Criteria Document, has also taken a stand, although in a recommendation rather than a policy format. One should keep in mind that these conclusions, reached independently in several parts of the world, were not decided lightly, but only after careful review of all available data by physicians, epidemiologists, basic scientists, and biostatisticians within and outside government.

It remains for each of us to reach our own personal decision after carefully appraising the existing data, evaluating the level of projected risk, and considering available preventive measures. In making the decision we must further weigh risk against cost, practicality against zeal, and personal concern against disinvolvement—certainly a difficult task given less than perfect information.

Despite these difficult considerations, many of us have already reached our decision, ie, to act positively to minimize anesthetic exposure without waiting for the final ultimate proof. It would seem preferable to have acted than to have lost our opportunity by ignoring the warning signs. The preventive cost is significant, but remains small by comparison to potential benefits.

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To the Editor:

I believe that the article by Dr. Ferstandig "Trace concentrations of anesthetic gases: a critical review of their disease potential" Anesth Analg 57:328-345, 1978 does a disservice to the area of investigation it reviews. The disservice is a consequence of factual error and faulty logic. The result is in many cases a misinterpretation of the evidence. There follows an illustration of these defects. On page 331, Dr. Ferstandig wrote:

> "Stevens et al[57] compared toxicities of low levels of halothane, isoflurane, and ether in mice, rats and guinea pigs, and later also studied fluroxene, enflurane, and N_2O.[58] The animals were exposed to 0.001 to 0.1 MAC for 7 hours per day, 5 days per week for up to 7 weeks. The authors found reduced weight gain in some animals and increased gain in others, as well as occasional liver and kidney damage. The lack of consistent findings in both studies may be related to unexplained high death rates which were not correlated to experimental treatment."

The second sentence contains a factual error. The animals were exposed continuously rather than 7 hours per day, 5 days per week.

The third sentence implies and the fourth sentence explicitly states that the results from the 2 studies by Stevens et al were inconsistent. The data don't support this assertion. For example, it is true that some experimental groups of animals gained less weight than their control peers while the reverse was true in other groups. Such would be expected in the 200 comparisons made between control and experimental groups. What Dr. Ferstandig ignores is that in the 200 comparisons, only 4 showed experimental groups to gain significantly more than their control peers whereas 60 gained significantly less. Of the 60 comparisons showing a lesser gain than control animals, 43 were in the halothane and fluroxene groups and in these groups, failure to gain weight was directly related to anesthetic dose. Indeed, the highest doses of the other anesthetics also impaired growth but these doses were 10 to 100 times greater than the doses of halothane or fluroxene which impaired growth.

Dr. Ferstandig glosses over the liver injury found by Stevens and coworkers. Liver injury was more than "occasional" and appeared at higher anesthetic concentrations with each agent except fluroxene where the higher concentrations proved lethal. The point made by Stevens et al (and overlooked by Dr. Ferstandig) was that the concentrations of halothane which produced degenerative liver lesions were in the trace range (less than 100 parts per million) whereas the other anesthetics caused degenerative lesions at concentrations about 100 times greater (i.e. approaching anesthetic levels).

Finally, the "unexplained high death rates" were usually (but not always) correlated to experimental treatment. Fluroxene at concentrations exceeding 0.01% (i.e. about 1/600 MAC) killed all species. Lower concentrations exerted progressively less deadly effects. Higher concentrations of halothane also proved lethal to mice and guinea pigs. Rats survived exposure to all concentrations of all agents except fluroxene. The highest ether concentrations also killed mice and guinea pigs but these concentrations (in MAC units) were 10 times greater than the lethal halothane concentrations.

I could cite what I believe are other examples of error in fact and interpretation, but that would belabor my point. I agree with Dr. Ferstandig's position that the inhaled anesthetics (including halothane) are not significantly toxic as used today in the vast majority of patients. But, by overstating his case, Dr. Ferstandig calls his own conclusions into question.

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* * *

HAZARDS OF BOTTLE ADAPTORS FOR VAPORIZERS

To the Editor:

We wish to bring to the attention of anesthesia practitioners the potential hazard illustrated in the accompanying photographs. In fig 1, the orange "keyed bottle adaptor" for filling an enflurane vaporizer with a "pin safety system" is shown properly fitting onto a bottle of enflurane, interlocking with the orange plastic bottle collar. In fig 2, the same "keyed bottle adaptor" is



FIG 1

shown fitting onto a bottle of Abbott halothane U.S.P., which has the same label color as the adaptor and no plastic collar. The adaptor can be tightened sufficiently, particularly when new, to prevent leaks at the adaptor-bottle junction. This allows halothane to be poured into a "pin safety system" enflurane vaporizer with ease. Reiterating, three separate conditions combine to make a cross-fill mistake possible: (1) No collar is on the Abbott bottle. (2) The bottle neck is of such a diameter as to relatively easily accept the adaptor. (3) The Abbott bottle label is of the same color orange as the adaptor. This situation has lead, in our hospital, to return of this halothane U.S.P. product to the manufacturer. Fortunately, it was noted prior to any patient receiving a mixture of halothane-enflurane.

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* * *

PHYSOSTIGMINE REVERSAL OF HALOTHANE ANESTHESIA

To the Editor:

We have read with interest Dr. Horrigan's recent report[1] of the effect of physostigmine on MAC in dogs anesthetized with halothane. He noted transient antagonism of anesthesia in 5 of 6 dogs given physostigmine 0.04 mg/kg during halothane administration. Arousal was clinically evident 1 to 5 minutes after administration of physostigmine in spite of no decrease in end-tidal halothane concentration. Arousal lasted from 2 to 30 minutes, too short a period for MAC determination. MAC values subsequently determined 30 to 90 minutes after physostigmine administration were significantly less than control measurements. As a result of his observations, he suggests that physostigmine would not be "an effective antagonist to postoperative somnolence due to halothane" in patients. Unfortunately, he has "extrapolated" from results during ongoing anesthesia to the somnolent patient in the recovery area postanesthesia. The transient arousal of the patient somnolent after

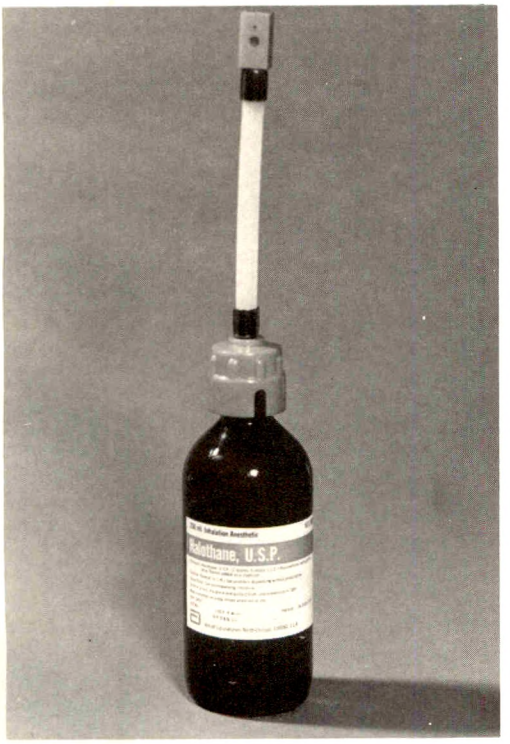


FIG 2

inhalational anesthesia might be expected to be accompanied by an alleviation of attendant respiratory depression. An increase in alveolar ventilation is doubtless the best means of alleviating the soporific effects of inhalational agents. Thirty minutes with or without an increase in alveolar ventilation might well be enough to permit excretion of sufficient volatile agent that the patient would remain awake when the physostigmine-induced arousal had waned.

In this connection we draw to your attention a recent report (published after acceptance of Dr. Horrigan's study) by Hill, Stanley, and Sentker.[2] In a double-blind study of 230 adult elective surgical patients who had undergone halothane anesthesia, they noted significant reversal of postoperative somnolence by physostigmine 2 mg IV.

It would appear that, contrary to Dr. Horrigan's suggestion, physostigmine may in fact be a useful adjunct in the treatment of postoperative somnolence due to halothane.

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John Brebner, MD, PhD
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2. Hill GE, Stanley TG, Sentker CR: Physostigmine reversal of postoperative somnolence. Can Anaesth Soc J 24:707-711, 1977

Dr. Horrigan offers the following reply:

To the Editor:

Thank you for sending me the letter from Drs. Drummond and Brebner regarding my paper on the interaction between physostigmine and halothane. They correctly point out the difference between ongoing halothane anesthesia which I studied and the decreasing level of halothane that is presumably occurring in the recovery room.

I know of no data on the effect of physostigmine on alveolar ventilation in patients emerging from anesthesia; if an increase occurs it should certainly hasten awakening, as Drs. Drummond and Brebner suggest.

The clinical study by Hill et al mentioned in the letter demonstrates a significant reversal by physostigmine of postanesthetic somnolence. The anesthetic technic employed in that study included atropine, secobarbital, thiopental, N_2O and halothane. Physostigmine did reverse the CNS depression produced by that combination of agents. Nausea and abdominal cramps occurred in 10% of the patients receiving physostigmine. El-Ganzouri et al, in a report of 34 patients receiving physostigmine postoperatively, found a 32% incidence of nausea and 21% incidence of vomiting (El-Ganzouri A, et al, Abstracts of Scientific Papers, American Society of Anesthesiologists Meeting, 1977).

Since the recovery time of patients is only minimally shortened by physostigmine (18 minutes in the study by Hill et al), the potential hazards of the drug should limit its use in the recovery period to carefully selected patients.

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* * *

INEXPENSIVE PRECORDIAL STETHOSCOPE

To the Editor:

Commonly, a patient's heart sounds are monitored during regional or general anesthesia, frequently employing a precordial stethoscope. Commercially available precordial stethoscopes are quite satisfactory, but they have the disadvantage of being expensive, particularly for a resident member of our profession and also for those physicians practicing in developing countries, where equipment and supplies might be a problem.

We have devised a way to make a quite satisfactory and virtually free precordial stethoscope (fig 1 and 2). A suitable screw-



FIG 1. Suitable bottle caps

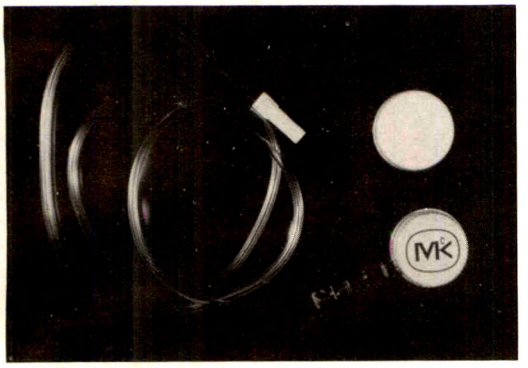


FIG 2. Cap with IV extension tubing inserted

cap bottle closure, such as that which would be removed from a bottle of IV fluid, irrigating fluid, or a drug, but which must have a rounded lower margin to avoid cutting the patient's skin, has a small hole made in one side of the cap with a sharp instrument. An IV extension tube is then inserted into the hole and connected to either a monaural earpiece or a binaural stethoscope and the precordial stethoscope is now functional. It is appropriately placed and taped to the patient's skin. This device has been used satisfactorily on several hundred patients and it compares favorably with commercially available units.

Construction of this device takes 2 to 3 minutes; and the cost is virtually nil since the bottle closure would normally be discarded and the IV extension set is at worst an inexpensive item, and at best a used one may be employed for this purpose. Additionally, this item has the advantage of being extremely light in weight.

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CARDIORESPIRATORY ARREST IN DIABETICS

Twelve cardiorespiratory arrests in 8 young diabetics with severe autonomic neuropathy are reported. One patient died at the time of the arrest, and 2 others died suddenly after returning home. There was no evidence of myocardial infarction, cardiac arrhythmia, or hypoglycemia at the time of arrest. In most episodes there was some interference with respiration, either by anesthesia, drugs, or bronchopneumonia. Five episodes occurred during or immediately after anesthesia. The arrests may have been caused by defective respiratory, rather than cardiovascular, reflexes. Cardiorespiratory arrest appears to be a specific feature of diabetic autonomic neuropathy and may contribute to mortality. *(Page MMcB, Watkins PJ: Cardiorespiratory arrest and diabetic autonomic neuropathy. Lancet 1:14-16, 1978)*

Book Reviews

Factors Influencing Vascular Reactivity, by Oliver Carrier and Shoji Shibata, 296 pp, New York, Igaku-Shoin Medical Publishers, Inc., 1977. Price $38.00.

The book presents 12 review type chapters by various authors on topics related to the physiology and pharmacology of the vascular system. One of the intended aims of the editors (Drs. Carrier and Shibata) was to give readers direction for future studies in vascular smooth muscle, and undoubtedly the book will be most valuable to investigators in this area. However, the more general reader will find this book informative and enjoyable.

The book is laid out in the traditional fashion with the beginning chapters devoted to the ultrastructure, and biochemistry of vascular smooth muscle. Both chapters are well written and the reference list at the end of each is not too formidable. In a separate chapter, Drs. Casteels and Raeymaekers discuss the effects of electrolytes on vascular reactivity. They give a lucid description of the origin of the membrane potential, and the factors that affect the concentration of cytoplasmic Ca^{++} in vascular smooth muscle. Catecholamine metabolism with special emphasis being given to uptake of catechols by the vascular cells is discussed in a separate chapter by Trendelenburg. The subject of drug receptors is discussed by Dr. Fleisch and, in this reader's opinion, this is one of the best chapters in the book.

In the section dealing with physiological factors, the section on vascular aging is particularly interesting to clinicians. The authors point out that in advanced old age adrenergic innervation of blood vessels is decreased, but that the vessels are hyporesponsive to adrenergic vasoactive compounds. The authors warn us against associating those two facts since it is well known that vascular tissue depleted of catecholamines is usually hyperresponsive to stimuli. In another part of this same chapter, Drs. Altura and Altura review the available literature on the effects of oral contraceptives and sex hormones on vascular reactivity. In general the material they have reviewed seems to indicate that estrogenic steroids can enhance vascular tone and responsiveness, whereas similar doses of progesterone either have no effect or tend to do the reverse. They go on to a point out, however, that although tissue and plasma levels of neurohumoral substances may be effected by sex hormones, too many gaps exist in our knowledge to preclude any definite conclusions at this time.

The effect of anesthetic or analgesic drugs on vascular reactivity is not discussed in this book which makes it a little disappointing to the anesthesiologist. However, the overall layout of the book is so pleasing and the selection of topics diverse enough that it will be enjoyed by both clinicians and researchers.

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* * *

Clinical Pharmacology, Second Edition, by Kenneth L. Melmon and Howard F. Morrelli, 1146 pp, New York, Macmillan Publishing Company, Inc, 1978. Price $25.00.

This textbook discusses the scientific basis for drug therapy. Therefore, it is an appropriate reference source for all physicans who treat patients with drugs. Forty-two authors discuss topics ranging from pharmacokinetics to the economics of drug use. The material presented is accurate, complete, current and well referenced.

Although none of the authors are anesthesiologists, the principles of clinical pharmacology cross specialty lines and can be appropriately applied to anesthesiology. Topics discussed that are of particular interest and value to anesthesiologists include the influence of disease states on drug choice, pharmacokinetics of drugs in the pregnant and pediatric patient and pharmacologic considerations in the presence of cardiovascular, respiratory and neurologic disorders. Detailed discussions of drug reactions and interactions, alcohol and drug abuse and management of deliberate or accidental drug overdose have special importance to the anesthesiologist.

A unique aspect of this textbook is the discussion of clinical pharmacology in relation to the symptoms and pathophysiology of the disease being treated. Therefore, this textbook may be a more appropriate reference source for the clinician than traditional pharmacology textbooks.

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* * *

Monitoring in Anesthesia, by Lawrence J. Saidman and N. Ty Smith, 356 pp, Sumerset, John Wiley & Sons, Inc., 1978. Price $25.00.

The supervision of patients who are anesthetized is becoming more complex and difficult and more expensive and even more dangerous with every passing year. Most anesthesiologists now agree that inspection, palpation, and auscultation are no longer sufficient and that in many instances machines have to be employed to gather the signals that we use to make our often repeated diagnoses of depth of anesthesia, adequacy of ventilation, circulation, motor function and temperature.

This book discusses not only how to monitor but in many instances why to monitor and it does all of this quite well. It goes into maternal and fetal monitoring, the measurement of gases in the atmosphere of the operating room, electrical safety, computers and projections into the future.

To test the value of the book for the clinical anesthesiologist, I asked the question whether this volume would help me were I charged with selecting ECG monitors for a new operating room suite. I started with the index and looked under electrocardiography but found only eight entries which did an injustice to the contents of the book which has many more places where the principles and machines subserving electrocardiography are discussed. There is a chapter on "Monitoring of the Cardiovascular System" by Prys Robert, another on "Noninvasive Monitoring" by Reitan, one on "Selection of Monitoring Equipment" by Noble and Kostinsky, and one on "Electrical Safety" by Meathe, all of which have useful hints related to electrocardiography in the operating room. After studying these chapters one would walk away much better informed and more worried. The worry because the book discusses the limitations of electrocardiography and the dangers without really giving a final prescription on how to make electrical monitoring in the operating room fool-proof and utterly safe for the patient. Perhaps that is impossible with current technology and perhaps the message is that monitoring using fancy machinery extracts a price for the valuable information that it provides.

A similar test applied to the question whether or not I would become a better student of blood pressure recordings in the operating room was also passed with satisfactory marks by this little book. The whys and hows of manual and electronic blood pressure recordings are well described and would be useful to anyone who has to worry about getting more than a rough estimate of systolic and diastolic pressure, the sort of estimate most of us are satisfied with in the operating room.

Because almost a score of contributors have written the chapters of this book, some unevenness, a few mistakes, and some overlap is inevitable. The all too parsimonious index is perhaps the book's greatest flaw. But these weaknesses are really rather insignificant. The information packed in these 350 pages are well presented, nicely illustrated, and fun to read. While not every anesthesiologist may want to have this volume in his or her personal library, it certainly should be readily accessible to anesthesiologists who worry about monitoring i e, all clinically active anesthesiologists.

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Title	Author/Editor	Publisher	Price Pages
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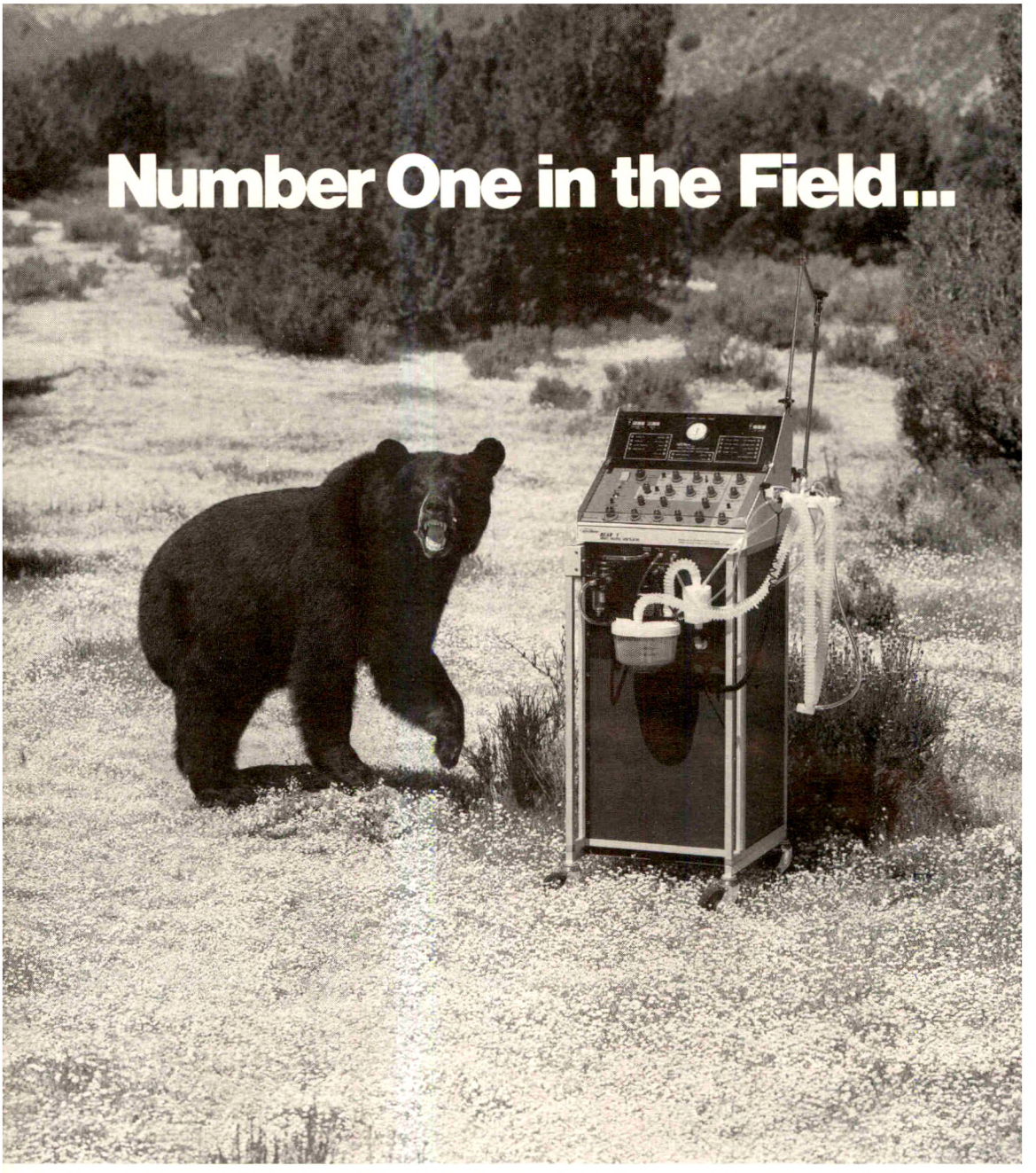
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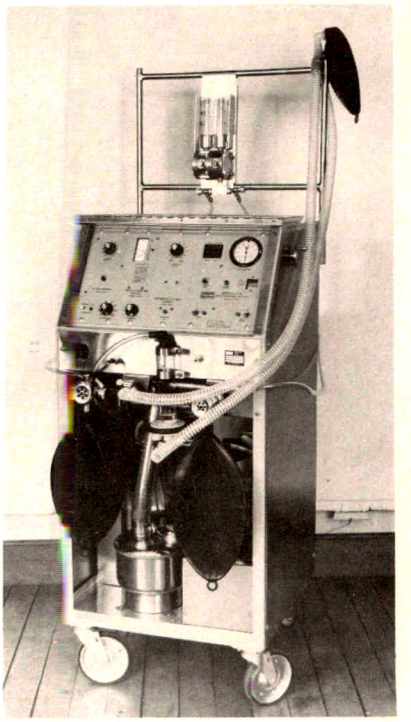
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At first the ventilator is generally set to supply mandatory breaths at a normal controlled rate. This controlled respiration is then gradually changed, by lengthening the interval between breaths (a second or two at a time) as the patient's condition improves. Eventually mandatory breaths are spaced so far apart that the patient scarcely relies on them at all — and "weaning" is completed.[2]

VERSUS ASSIST

Triggering an assistor has often been a problem, particularly for infants, since their rates are rapid and their inspiratory impulses are slight. If synchronization is less than perfect, the patient inhales (at least part of the time) with no fresh gas available. Under such circumstances, blood levels of CO_2 rise, as noted by Kirby and associates.[1]

VERSUS CONTROL

For apneic patients, control is obviously needed. But to take over, when a patient is breathing spontaneously, drugs have to be used or the patient has to be hyperventilated. Either procedure has drawbacks. Paralytic or sedative agents may obscure signs of neurological or metabloic disorders. Lowered muscle tone may impair venous return, and hence cardiac output. The effects of such drugs are particularly hard to predict in infants.

Hyperventilation (often used to suppress spontaneous breathing efforts) has drawbacks, too. The resultant alkalosis reduces cerebral blood flow. Blood levels of calcium and magnesium are altered. Airway resistance increases and pulmonary compliance decreases with hypocarbia.[3] Finally, there is evidence of a shift in the carbon dioxide response curve, which makes weaning more difficult.

All of these pit-falls can be avoided by using continuous-flow IMV.

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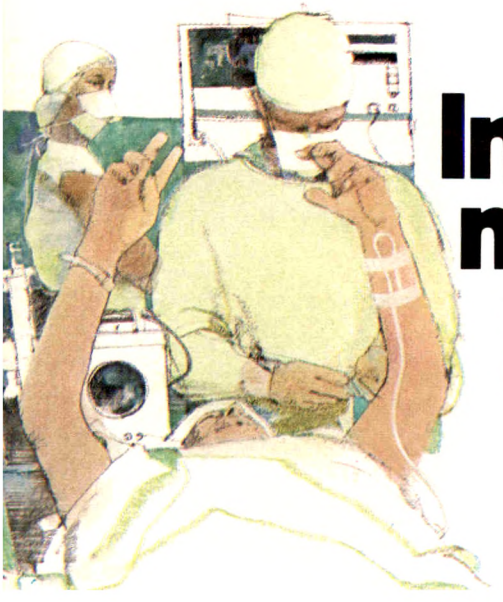
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INDICATIONS SUBLIMAZE (fentanyl) is indicated:

– for analgesic action of short duration during the anesthetic periods, premedication, induction, and maintenance, and in the immediate postoperative period (recovery room) as the need arises.

– for use as a narcotic analgesic supplement in general or regional anesthesia.

– for administration with a neuroleptic such as *INAPSINE*® (droperidol) injection as an anesthetic premedication, for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia.

CONTRAINDICATIONS SUBLIMAZE (fentanyl) is contraindicated in patients with known intolerance to the drug.

WARNINGS AS WITH OTHER CNS DEPRESSANTS, PATIENTS WHO HAVE RECEIVED SUBLIMAZE (fentanyl) SHOULD HAVE APPROPRIATE SURVEILLANCE.

RESUSCITATIVE EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

See also discussion of narcotic antagonists in Precautions and Overdosage.

If SUBLIMAZE (fentanyl) is administered with a tranquilizer such as *INAPSINE* (droperidol), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used *fluids and other countermeasures to manage hypotension should be available.*

As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE (fentanyl) persists longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as 1/4 to 1/3 those usually recommended. SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. The effect is related to the speed of injection and its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

Drug Dependence – SUBLIMAZE (fentanyl) can produce drug dependence of the morphine type and therefore has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE (fentanyl) in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure – SUBLIMAZE (fentanyl) should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition, SUBLIMAZE (fentanyl) may obscure the clinical course of patients with head injury.

Usage in Children – The safety of SUBLIMAZE (fentanyl) in children younger than two years of age has not been established.

Usage in Pregnancy – The safe use of SUBLIMAZE (fentanyl) has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

PRECAUTIONS *The initial dose of SUBLIMAZE (fentanyl) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses.*

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms (see Actions) SUBLIMAZE (fentanyl) can also alter respiration. Therefore, when SUBLIMAZE (fentanyl) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia. When used with a tranquilizer such as *INAPSINE* (droperidol), blood pressure may be altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE (fentanyl) should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory res and others with potentially compromised respiration. In such patients, narc may additionally decrease respiratory drive and increase airway resista During anesthesia, this can be managed by assisted or controlled respira Respiratory depression caused by narcotic analgesics can be reverse narcotic antagonists. Appropriate surveillance should be maintained bec the duration of respiratory depression of doses of fentanyl employed di anesthesia may be longer than the duration of the narcotic antagonist ac Consult individual prescribing information (levallorphan, nalorphine naloxone) before employing narcotic antagonists.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIM (fentanyl), pulmonary arterial pressure may be decreased. This fact shoul considered by those who conduct diagnostic and surgical procedures w interpretation of pulmonary arterial pressure measurements might deter final management of the patient.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, general anesthetics) will have additive or potentiating effects with SUBLIM (fentanyl). When patients have received such drugs, the dose of SUBLIM (fentanyl) required will be less than usual. Likewise, following the admini tion of SUBLIMAZE (fentanyl), the dose of other CNS depressant drugs sh be reduced.

SUBLIMAZE (fentanyl) should be administered with caution to patients with and kidney dysfunction because of the importance of these organs ir metabolism and excretion of drugs.

SUBLIMAZE (fentanyl) may produce bradycardia, which may be treated atropine; however, SUBLIMAZE (fentanyl) should be used with caution ir tients with cardiac bradyarrhythmias.

When SUBLIMAZE (fentanyl) is used with a tranquilizer such as *INAP* (droperidol), hypotension can occur. If this occurs, the possibili hypovolemia should also be considered and managed with appropriate p teral fluid therapy. Repositioning the patient to improve venous return t heart should be considered when operative conditions permit. Care shoul exercised in moving and positioning of patients because of the possibil orthostatic hypotension. If volume expansion with fluids plus other counter sures do not correct hypotension, the administration of pressor agents than epinephrine should be considered. Because of the alpha-adrene blocking action of *INAPSINE* (droperidol), epinephrine may paradoxically crease the blood pressure in patients treated with *INAPSINE* (droperidol When *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) and the EE used for postoperative monitoring, it may be found that the EEG pattern ret to normal slowly.

ADVERSE REACTIONS As with other narcotic analgesics, the most com serious adverse reactions reported to occur with SUBLIMAZE (fentanyl respiratory depression, apnea, muscular rigidity, and bradycardia; if t remain untreated, respiratory arrest, circulatory depression or cardiac a could occur.

Other adverse reactions that have been reported are hypotension, dizzir blurred vision, nausea, emesis, laryngospasm, and diaphoresis.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIM (fentanyl), the following adverse reactions can occur: chills and/or shive restlessness, and postoperative hallucinatory episodes (sometimes associ with transient periods of mental depression); extrapyramidal symptoms tonia, akathisia, and oculogyric crisis) have been observed up to 24 h postoperatively. When they occur, extrapyramidal symptoms can usuall controlled with anti-Parkinson agents. Postoperative drowsiness is alsc quently reported following the use of *INAPSINE* (droperidol).

Elevated blood pressure, with and without pre-existing hypertension, has l reported following administration of SUBLIMAZE (fentanyl) combined wit *APSINE* (droperidol). This might be due to unexplained alterations in syr thetic activity following large doses; however, it is also frequently attribute anesthetic and surgical stimulation during light anesthesia.

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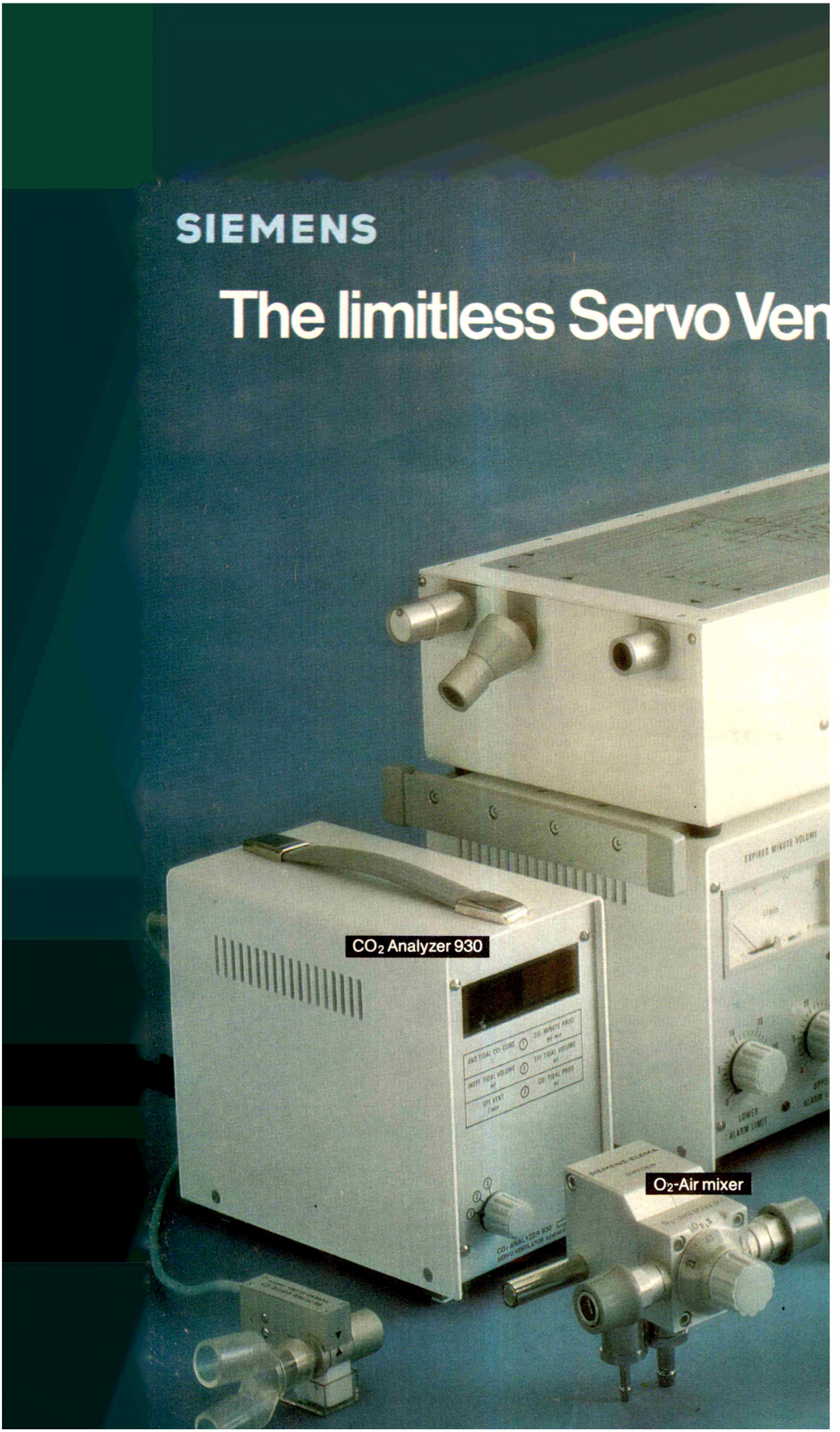
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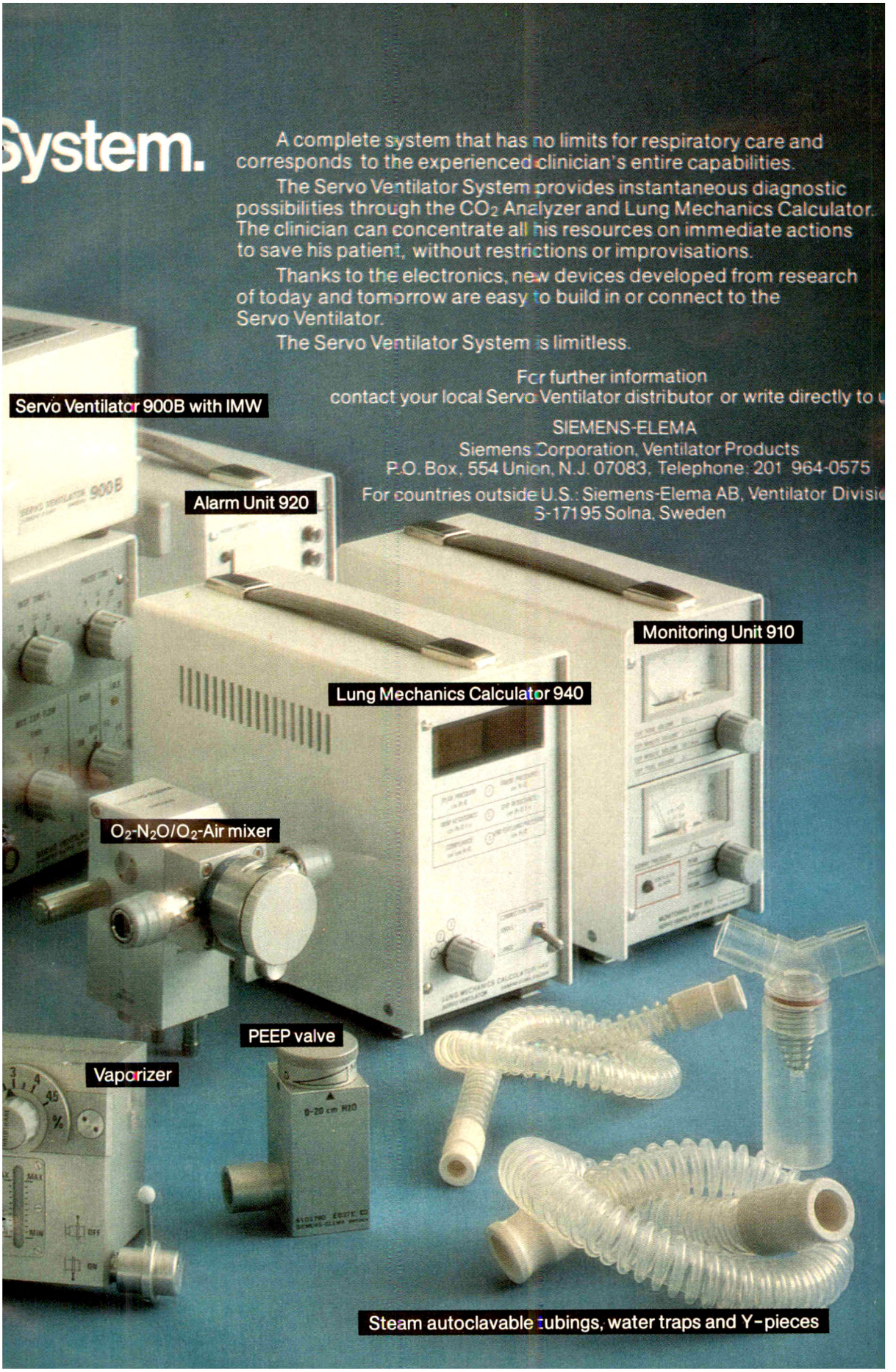
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This program is presented by the University of California in San Francisco and the University of California in Los Angeles Department of Anesthesiology, and is sponsored by Extended Programs in Medical Education of the University of California School of Medicine, San Francisco, California. This program is approved for Category 1 credit.

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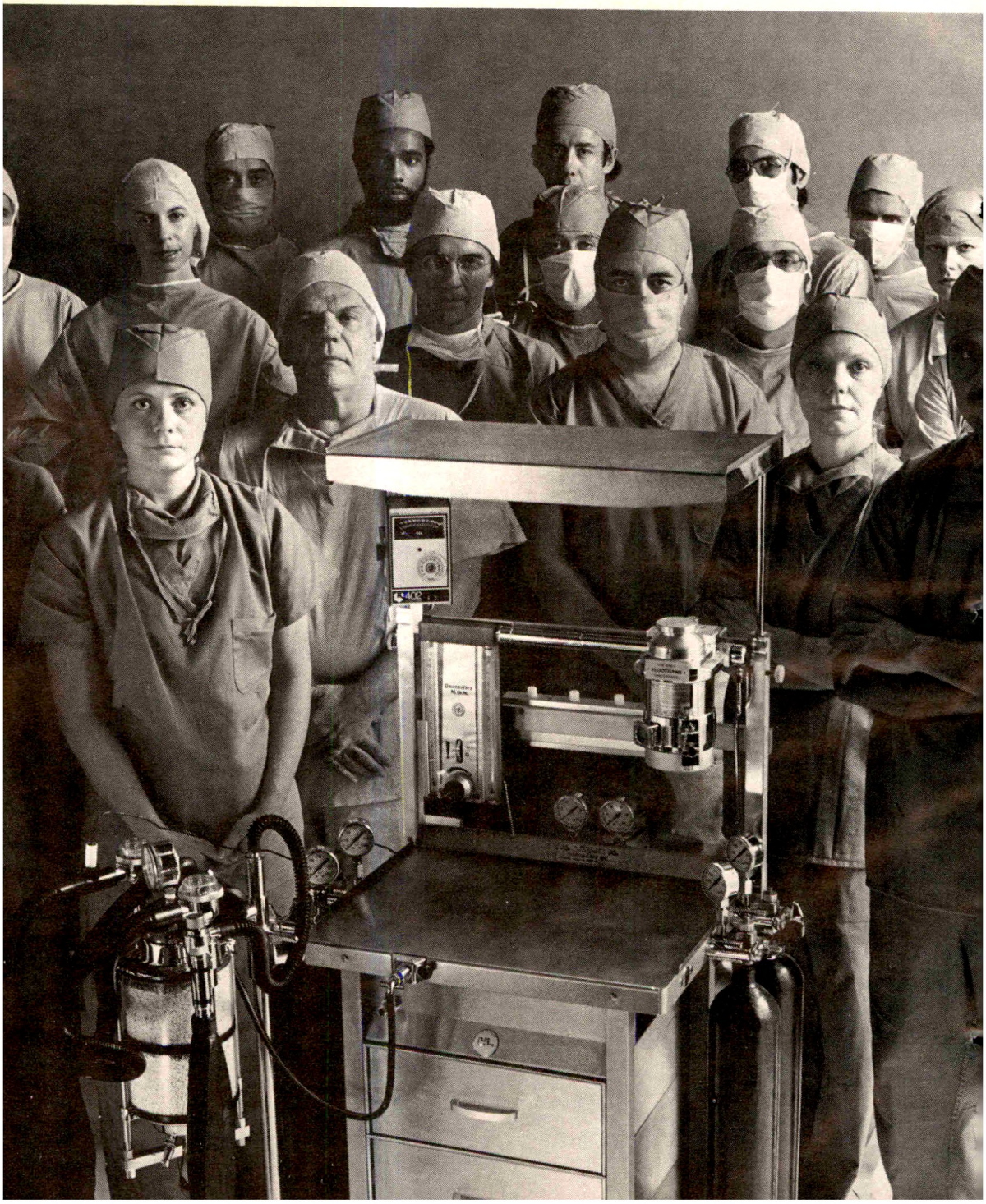
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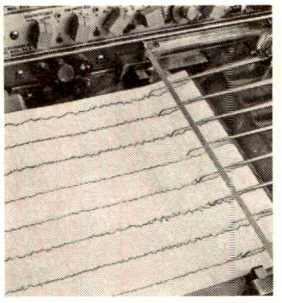
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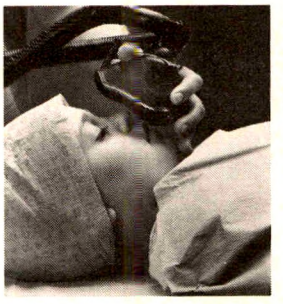
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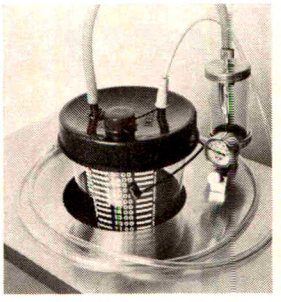
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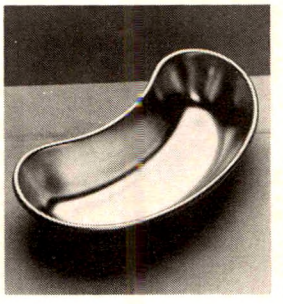




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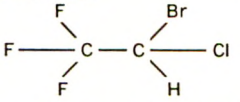
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Description. FLUOTHANE, brand of halothane, U.S.P., is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:



The specific gravity is 1.872-1.877 at 20° C, and the boiling point (range) is 49° C-51° C at 760 mm Hg. The vapor pressure is 243 mm Hg at 20° C. The blood/gas coefficient is 2.5 at 37° C, and the olive oil/water coefficient is 220 at 37° C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane, U.S.P.) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all the diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE (halothane, U.S.P.) is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy. Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane, U.S.P.) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

Adverse Reactions. The following adverse reactions have been reported: hepatic necrosis, cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide.

How Supplied. No. 3125—Unit packages of 125 ml and 250 ml of halothane, U.S.P. stabilized with 0.01% thymol (w/w).

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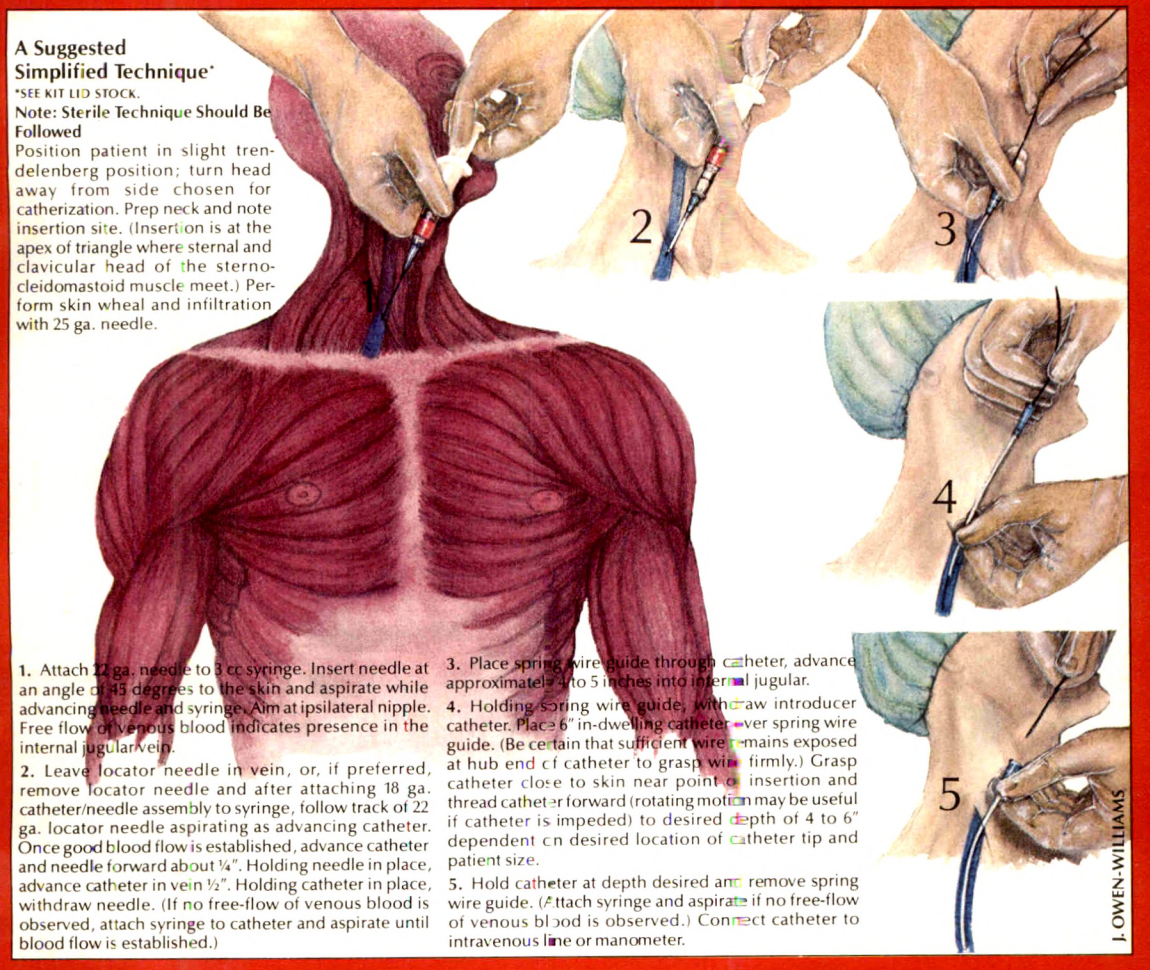
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3. Place spring wire guide through catheter, advance approximately 4 to 5 inches into internal jugular.

4. Holding spring wire guide, withdraw introducer catheter. Place 6" in-dwelling catheter over spring wire guide. (Be certain that sufficient wire remains exposed at hub end of catheter to grasp wire firmly.) Grasp catheter close to skin near point of insertion and thread catheter forward (rotating motion may be useful if catheter is impeded) to desired depth of 4 to 6" dependent on desired location of catheter tip and patient size.

5. Hold catheter at depth desired and remove spring wire guide. (Attach syringe and aspirate if no free-flow of venous blood is observed.) Connect catheter to intravenous line or manometer.

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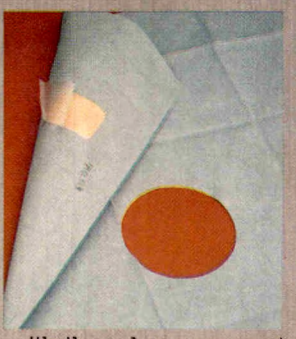
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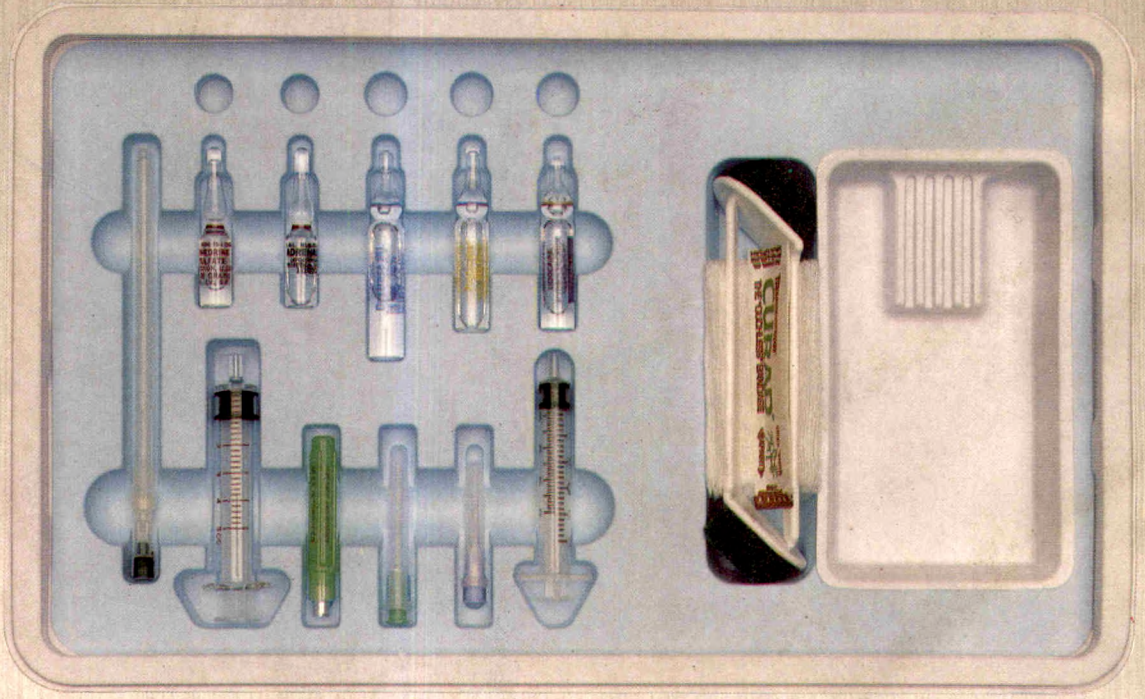
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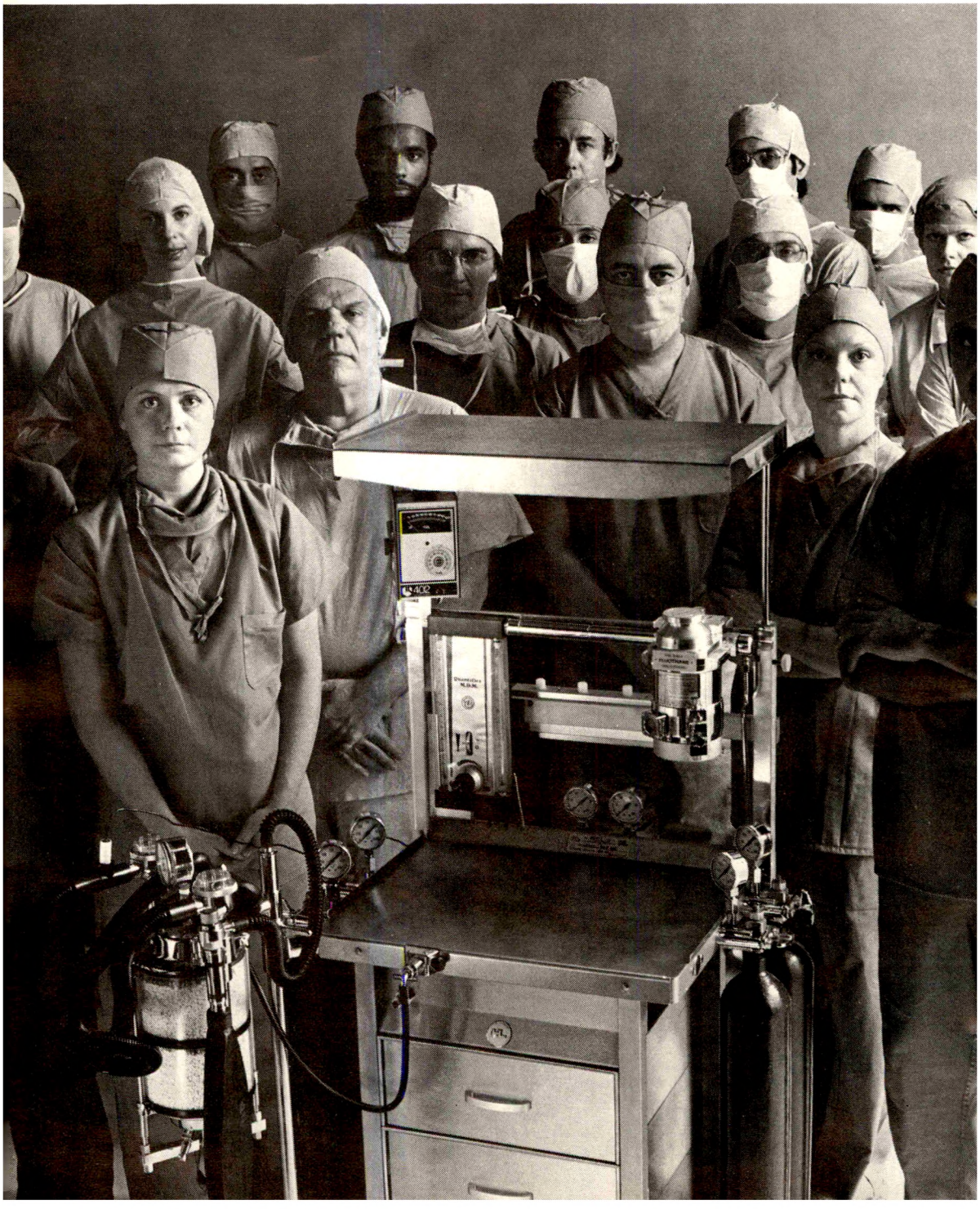
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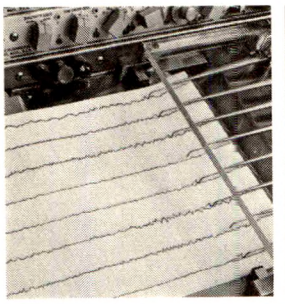
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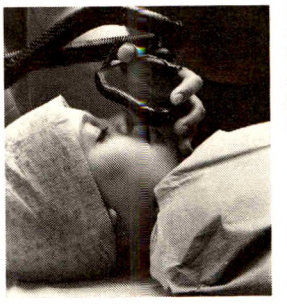
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EEG patterns indicative of cortical seizure activity which may be associated with clonic-tonic muscle activity have not been reported with the use of FLUOTHANE (halothane, U.S.P.)

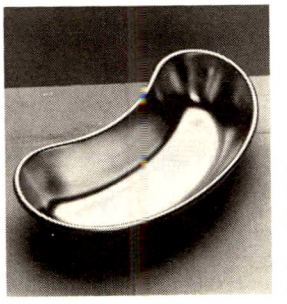




Rapid, smooth induction — particularly important in pediatric surgery — is facilitated by the pleasant odor of FLUOTHANE.

No increase in salivary or bronchial secretions is produced with FLUOTHANE.





Emergence is rapid and tranquil, with minimal nausea and vomiting* ...adjustment in the depth of anesthesia with FLUOTHANE is simple.

FLUOTHANE®
(halothane, U.S.P.)

the most widely used inhalation anesthetic in the world... over 110 million administrations in the U.S. alone

Ayerst®

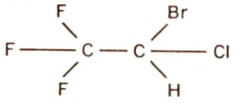
*See following page for full prescribing information.

for a variety of procedures, for a lot of good reasons

FLUOTHANE®
(halothane, U.S.P.)
the most widely used inhalation anesthetic in the world

(Complete text of package circular.)

Description. FLUOTHANE, brand of halothane, U.S.P., is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:



The specific gravity is 1.872-1.877 at 20° C, and the boiling point (range) is 49° C-51° C at 760 mm Hg. The vapor pressure is 243 mm Hg at 20° C. The blood/gas coefficient is 2.5 at 37° C, and the olive oil/water coefficient is 220 at 37° C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane, U.S.P.) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all the diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE (halothane, U.S.P.) is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy. Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane, U.S.P.) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

Adverse Reactions. The following adverse reactions have been reported: hepatic necrosis, cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide.

How Supplied. No. 3125—Unit packages of 125 ml and 250 ml of halothane, U.S.P. stabilized with 0.01% thymol (w/w).

7732

Ayerst Ayerst Laboratories
New York, N.Y. 10017

The best of all worlds



Dependable, lightweight, easy-to-use portable monitors, with multiple parameters and non-fade displays, working in your hospital where and when you need them providing increased capability per dollar invested.

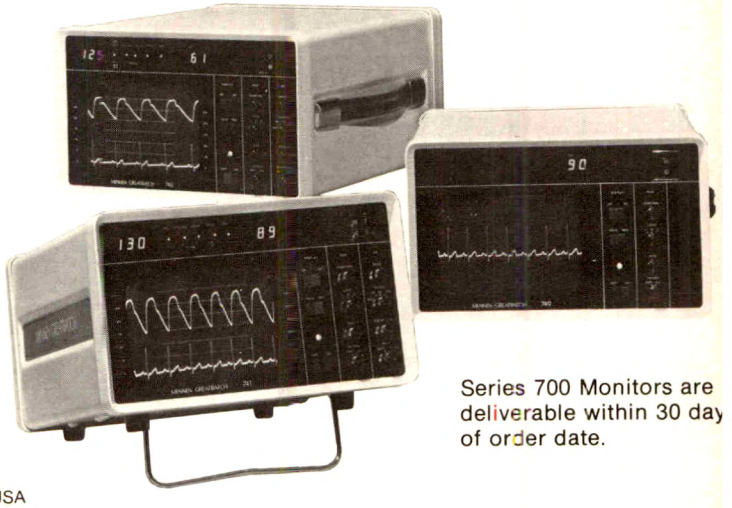
Bedside monitors in multi-patient systems that deliver vital patient data to central consoles and remote displays for economic systems monitoring, a cost-effectiveness that goes far beyond the price tag.

Bedside monitoring inputs to MENNEN GREATBATCH microprocessor assisted hemodynamic and patient data management systems or any other computer based system when equipped with the optional built-in ASCII Link, a dollar saving compatibility.

Superior performance and reliability means that the monitor is on the job working for you at all times, yet when service is needed it can be performed easily and efficiently by your own hospital medical electronics technician or by one of our nationwide factory service groups.

Series 700 Portable Monitors from Mennen Greatbatch

MENNEN GREATBATCH, backed by years of experience in medical electronics, provides a continuing and total commitment to critical care monitoring. Our systems and portable instruments compliment one another in their application and are soundly supported by all necessary accessories and supplies.



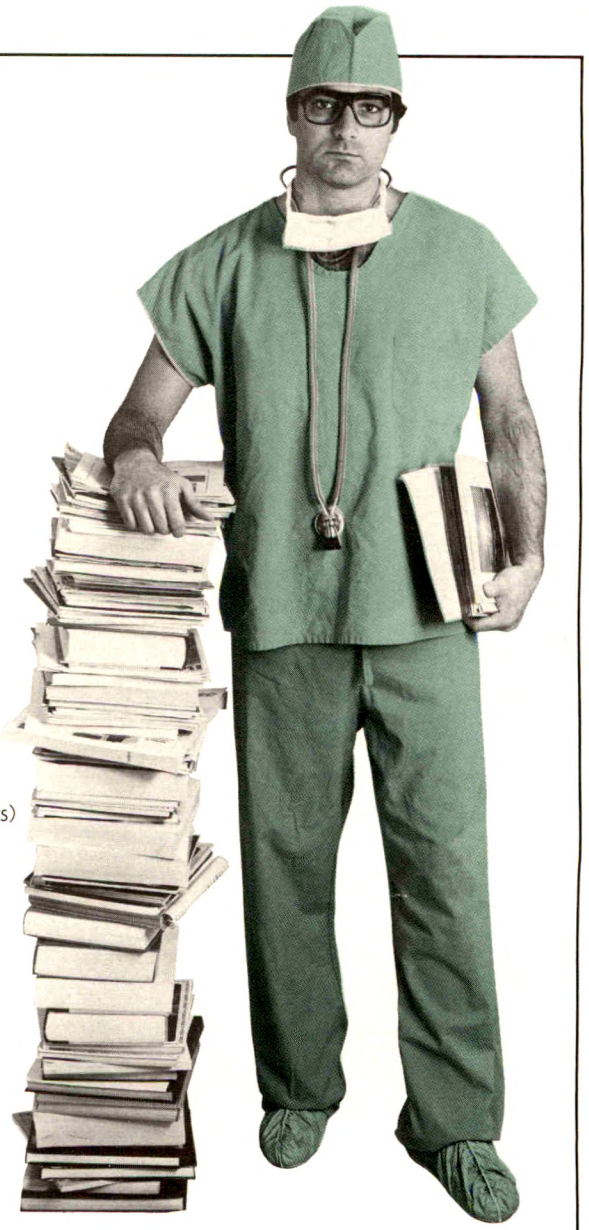
MENNEN GREATBATCH INC.

10123 MAIN STREET, CLARENCE, N.Y. 14031 USA
TELEPHONE 716 759-6921 TELEX 91-6402

Series 700 Monitors are deliverable within 30 day of order date.

Halothane U.S.P.

The "Familiar Territory" Anesthetic... Produced by Halocarbon Laboratories, Inc.



The OR is no place for surprises. Neither is the Recovery Room.

Years of experience and thousands of publications have made halothane the dependable agent you need. When you're looking for ease of administration and predictable results, halothane stands alone.

And, our Halothane U.S.P. helps keep hospital costs down.

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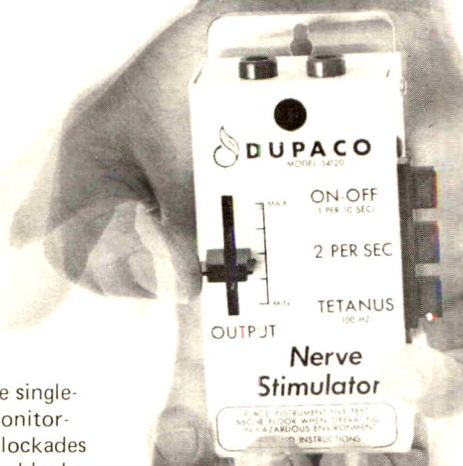
Halocarbon Laboratories, Inc.
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Hackensack, N.J. 07601
Telex: 134378

(We also offer savings on oxygen monitors)

Halothane – Still the world's standard.

The Dupaco NERVE STIMULATOR

Small, compact and versatile



Designed to facilitate single-hand operation in monitoring neuromuscular blockades and performing nerve blocks, the Dupaco Nerve Stimulator features three push-button switches to control all operating modes. The control knob for setting linear motion level also enables the operator to obtain reproducible outputs.

The three operating modes include a train-of-four pulses for monitoring neuromuscular blockade, a tetanus frequency of 100 Hz for a larger margin of safety in ensuring adequate reversal of neuromuscular blockade, and a stand-by frequency of 0.1 Hz.

Although the train-of-four mode is momentary for safety, it may be depressed for continuous function in performing nerve blocks.



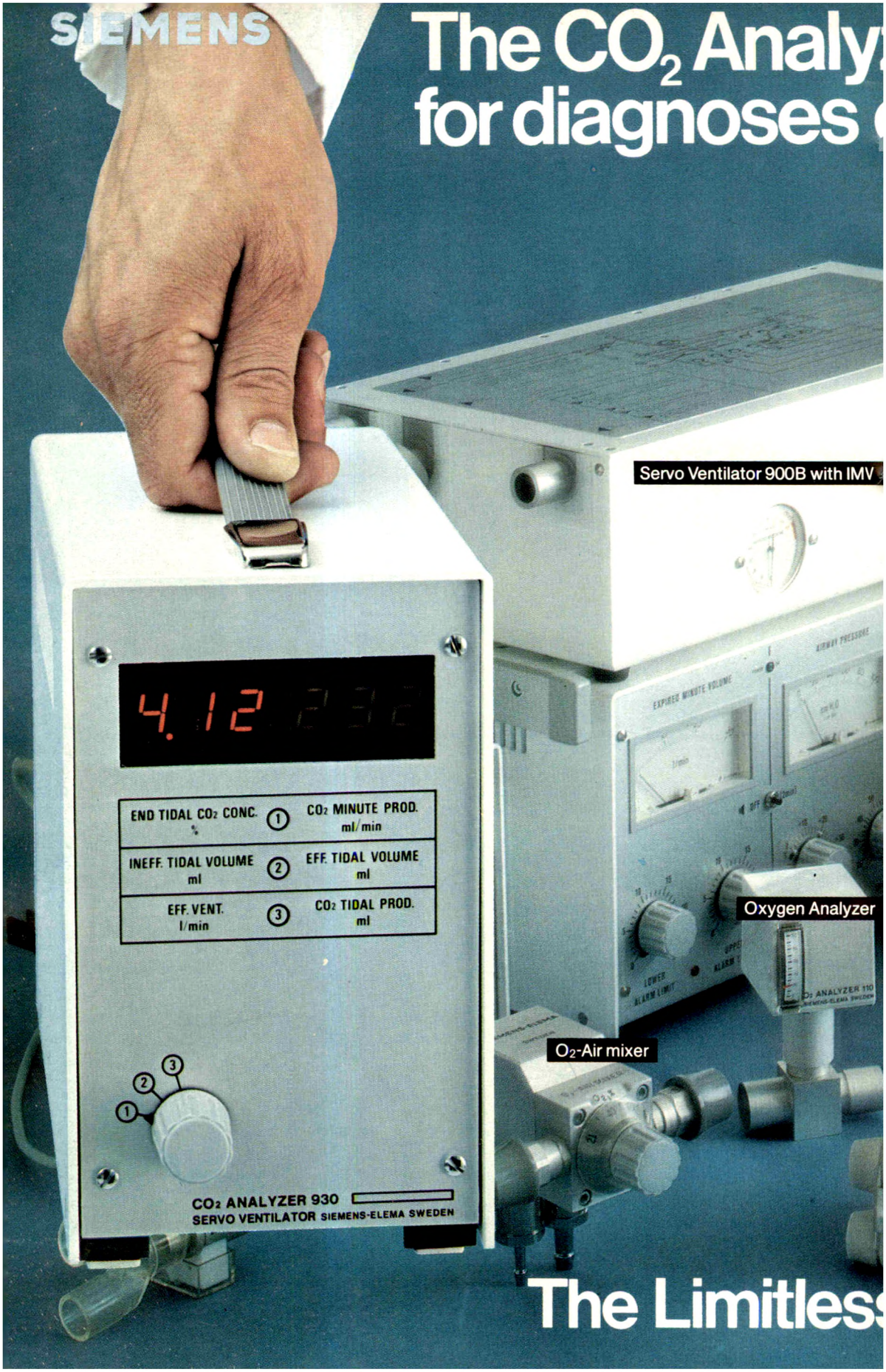
The Dupaco Nerve Stimulator features a neon pulse indicator which also serves as an on/off light, thereby extending the life of the battery.

In addition, a stainless steel clip doubles as battery compartment cover and a belt, linen or hook hanger.

The Dupaco Nerve Stimulator- small, compact and versatile because it has to be.

DUPACO

Post Office Box 98, San Marcos, Calif. 92069


SIEMENS
The CO_2 Analy
for diagnoses
Servo Ventilator 900B with IMV
Oxygen Analyzer
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END TIDAL CO_2 CONC. %
CO_2 MINUTE PROD. ml/min
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EFF. TIDAL VOLUME ml
EFF. VENT. l/min
CO_2 TIDAL PROD. ml
CO_2 ANALYZER 930
SERVO VENTILATOR SIEMENS-ELEMA SWEDEN
The Limitless

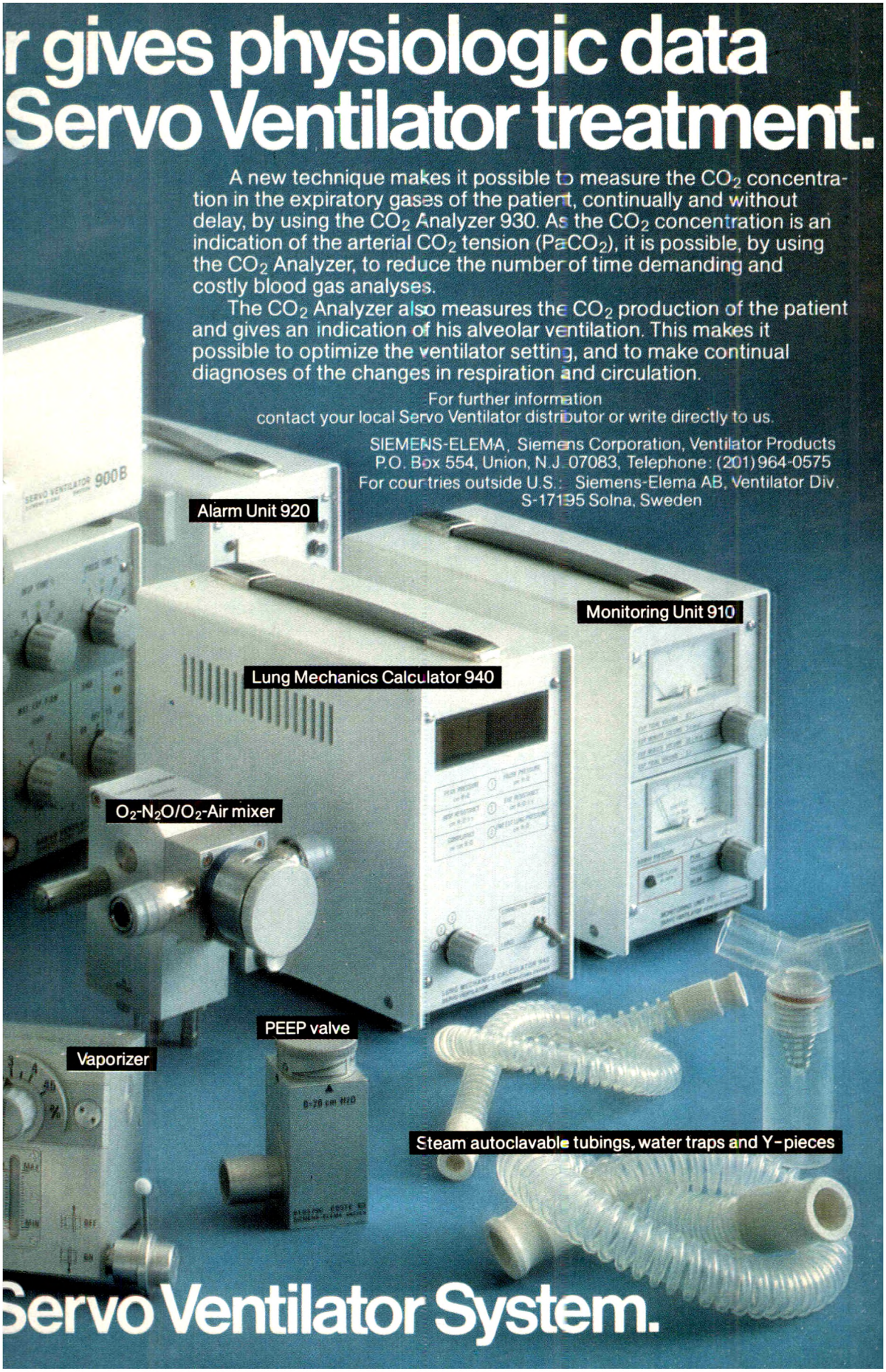
r gives physiologic data Servo Ventilator treatment.

A new technique makes it possible to measure the CO_2 concentration in the expiratory gases of the patient, continually and without delay, by using the CO_2 Analyzer 930. As the CO_2 concentration is an indication of the arterial CO_2 tension ($PaCO_2$), it is possible, by using the CO_2 Analyzer, to reduce the number of time demanding and costly blood gas analyses.

The CO_2 Analyzer also measures the CO_2 production of the patient and gives an indication of his alveolar ventilation. This makes it possible to optimize the ventilator setting, and to make continual diagnoses of the changes in respiration and circulation.

For further information
contact your local Servo Ventilator distributor or write directly to us.

SIEMENS-ELEMA, Siemens Corporation, Ventilator Products
P.O. Box 554, Union, N.J. 07083, Telephone: (201) 964-0575
For countries outside U.S.: Siemens-Elema AB, Ventilator Div.
S-17195 Solna, Sweden



Servo Ventilator System.


YOU KNOW THE POSITIVE SIDE OF
NARCOTIC-SUPPLEMENTED ANESTHESIA.
TITRATES THE RESPIRATORY DEPRESSION OUT

NARCAN®
naloxone HCl
NEUTRALIZES THE NEGATIVE

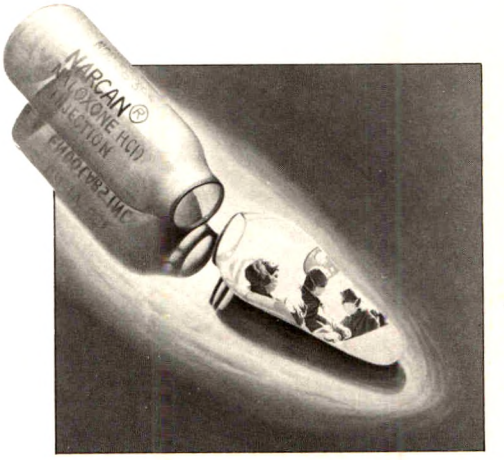
NARCAN® reverses narcotic-induced respiratory depression

- has no morphine-like activity
- will not cause any depression of its own or augment non-narcotic depression
- dosage can be titrated to reverse respiratory depression and maintain adequate analgesia

Useful when narcotic/N_2O anesthesia is employed

Potent, reliable and fast acting

- response is usually evident within 2-3 minutes after I.V. administration and only slightly longer I.M.
- can be used I.V., I.M. or subcutaneously according to the patient's need for immediacy and duration of narcotic antagonism



The duration of activity of some narcotics may exceed that of NARCAN.® Observe the patient closely and give repeat doses of NARCAN® if needed.

Also available, NARCAN® NEONATAL naloxone HCl

Please see next page for complete prescribing information.

Endo Laboratories, Inc.
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, New York 11530

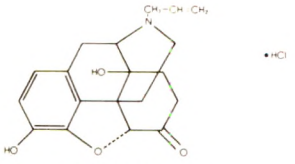
DUPONT

NARCAN® is an Endo registered U.S. trademark; U.S. Pat. 3,254,088

OF NARCOTIC-SUPPLEMENTED ANESTHESIA

NARCAN®
naloxone HCl

DESCRIPTION NARCAN* (naloxone hydrochloride), a narcotic antagonist, is a synthetic congener of oxymorphone. In structure it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.



NALOXONE HYDROCHLORIDE
(-)-17-Allyl-4, 5α-epoxy-3, 14-
dihydroxymorphinan-6-one hydrochloride

Naloxone hydrochloride occurs as slightly off-white crystals, and is soluble in water, slightly soluble in alcohol and practically insoluble in ether.

NARCAN* (naloxone hydrochloride) Injection is available in two concentrations, 0.02 mg and 0.4 mg of naloxone hydrochloride per ml. Each ml of either strength contains 8.6 mg of sodium chloride; and 2.0 mg of methylparaben and propylparaben as preservatives in a ratio of 9 to 1. pH is adjusted with hydrochloric acid.

ACTIONS NARCAN* (naloxone hydrochloride) is an essentially pure narcotic antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other narcotic antagonists; NARCAN* (naloxone hydrochloride) does not produce respiratory depression, psychotomimetic effects or pupillary constriction. In the absence of narcotics or agonistic effects of other narcotic antagonists it exhibits essentially no pharmacologic activity.

In the presence of physical dependence on narcotics NARCAN* (naloxone hydrochloride) will produce withdrawal symptoms; it has not been shown to produce tolerance nor to cause physical or psychological dependence.

When NARCAN* (naloxone hydrochloride) is administered intravenously the onset of action is generally apparent within two minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration of NARCAN* (naloxone hydrochloride). Intramuscular administration produces a more prolonged effect than intravenous administration. The requirement for repeat doses of NARCAN* (naloxone hydrochloride), however, will also be dependent upon the amount, type and route of administration of the narcotic being antagonized.

INDICATIONS NARCAN* (naloxone hydrochloride) is indicated for the complete or partial reversal of narcotic depression, including respiratory depression, induced by natural and synthetic narcotics, propoxyphene and the narcotic-antagonist analgesic pentazocine. NARCAN* (naloxone hydrochloride) is also indicated for the diagnosis of suspected acute opiate overdosage.

CONTRAINDICATIONS NARCAN* (naloxone hydrochloride) is contraindicated in patients known to be hypersensitive to it.

WARNINGS NARCAN* (naloxone hydrochloride) should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

The patient who has satisfactorily responded to NARCAN* (naloxone hydrochloride) should be kept under continued surveillance and repeated doses of NARCAN* (naloxone hydrochloride) should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN* (naloxone hydrochloride).

NARCAN* (naloxone hydrochloride) is not effective against respiratory depression due to non-opioid drugs.

Usage in Pregnancy Safe use of NARCAN* (naloxone hydrochloride) during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or other embryotoxic effects (See ANIMAL PHARMACOLOGY AND TOXICOLOGY). However, NARCAN* (naloxone hydrochloride) should be administered to pregnant patients only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS In addition to NARCAN* (naloxone hydrochloride), other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning.

In an isolated report two patients with pre-existing ventricular irritability requiring lidocaine, and either isoproterenol or epinephrine for hypotension following cardiopulmonary bypass procedures, developed ventricular tachycardia or fibrillation when given NARCAN* (naloxone hydrochloride) I.V. at 9 and 14 hours, respectively, postoperatively for persistent unresponsiveness. Although a direct cause and effect relationship has not been established, NARCAN* (naloxone hydrochloride) should be used with caution in patients with cardiac irritability.

ADVERSE REACTIONS In rare instances nausea and vomiting have been reported in postoperative patients receiving NARCAN* (naloxone hydrochloride) in doses higher than that recommended; a cause and effect relationship has not been established.

DOSAGE AND ADMINISTRATION NARCAN* (naloxone hydrochloride) may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of NARCAN* (naloxone hydrochloride) the patient should be kept under continued surveillance and repeated doses of NARCAN* (naloxone hydrochloride) should be administered, as necessary.

USAGE IN ADULTS Narcotic Overdose—Known or Suspected The usual initial adult dose is 0.4 mg (1 ml) NARCAN* (naloxone hydrochloride) administered I.V., I.M. or S.C. If the desired degree of counteraction and improvement in respiratory function is not obtained immediately following I.V. administration, it may be repeated intravenously at 2 to 3 minute intervals. Failure to obtain significant improvement after 2 or 3 doses suggests that the condition may be due partly or completely to other disease processes or non-opioid drugs.

Post Operative Narcotic Depression For the partial reversal of narcotic depression following the use of narcotics during surgery, smaller doses of NARCAN* (naloxone hydrochloride) are usually sufficient. The dose of NARCAN* (naloxone hydrochloride) should be titrated according to the patient's response. Excessive dosage of NARCAN* (naloxone hydrochloride) may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating or tachycardia.

For the initial reversal of respiratory depression, NARCAN* (naloxone hydrochloride) should be injected in increments of 0.1 to 0.2 mg intravenously at two to three minute intervals to the desired degree of reversal i.e., adequate ventilation and alertness without significant pain or discomfort.

Repeat doses of NARCAN* (naloxone hydrochloride) may be required within one to two hour intervals depending upon the amount, type (i.e., short or long acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

USAGE IN CHILDREN Narcotic Overdose—Known or Suspected The usual initial child dose is 0.01 mg/kg body weight given I.V., I.M. or S.C. This dose may be repeated in accordance with the adult administration guideline. If necessary, NARCAN* (naloxone hydrochloride) can be diluted with sterile water for injection.

USAGE IN NEONATES Narcotic-induced depression The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M. or S.C. This dose may be repeated in accordance with adult administration guidelines.

HOW SUPPLIED 0.4 mg/ml of NARCAN* (naloxone hydrochloride) for intravenous, intramuscular and subcutaneous administration.

Available in 1 ml ampuls in boxes of 10 and 100.

0.02 mg/ml of NARCAN* (naloxone hydrochloride) NEONATAL INJECTION for intravenous, intramuscular and subcutaneous administration.

Available in 2 ml ampuls in boxes of 10 and 100 ampuls.

ANIMAL PHARMACOLOGY AND TOXICOLOGY In the mouse and rat the intravenous LD_{50} is 150 ±5 mg/kg and 109 ±4 mg/kg respectively. In acute subcutaneous toxicity studies in newborn rats the LD_{50} (95% CL) is 260 (228-296) mg/kg. Subcutaneous injection of 100 mg/kg/day in rats for 3 weeks produced only transient salivation and partial ptosis following injections; no toxic effects were seen at 10 mg/kg/day for 3 weeks.

Reproductive studies including fertility, general reproductive performance, embryotoxicity, teratogenicity, and lactation did not show any abnormality in mice and rats at 10 mg/kg/day.

Endo Laboratories, Inc.
Subsidiary of E.I. du Pont de Nemours & Co. (Inc.)
Garden City, N.Y. 11530

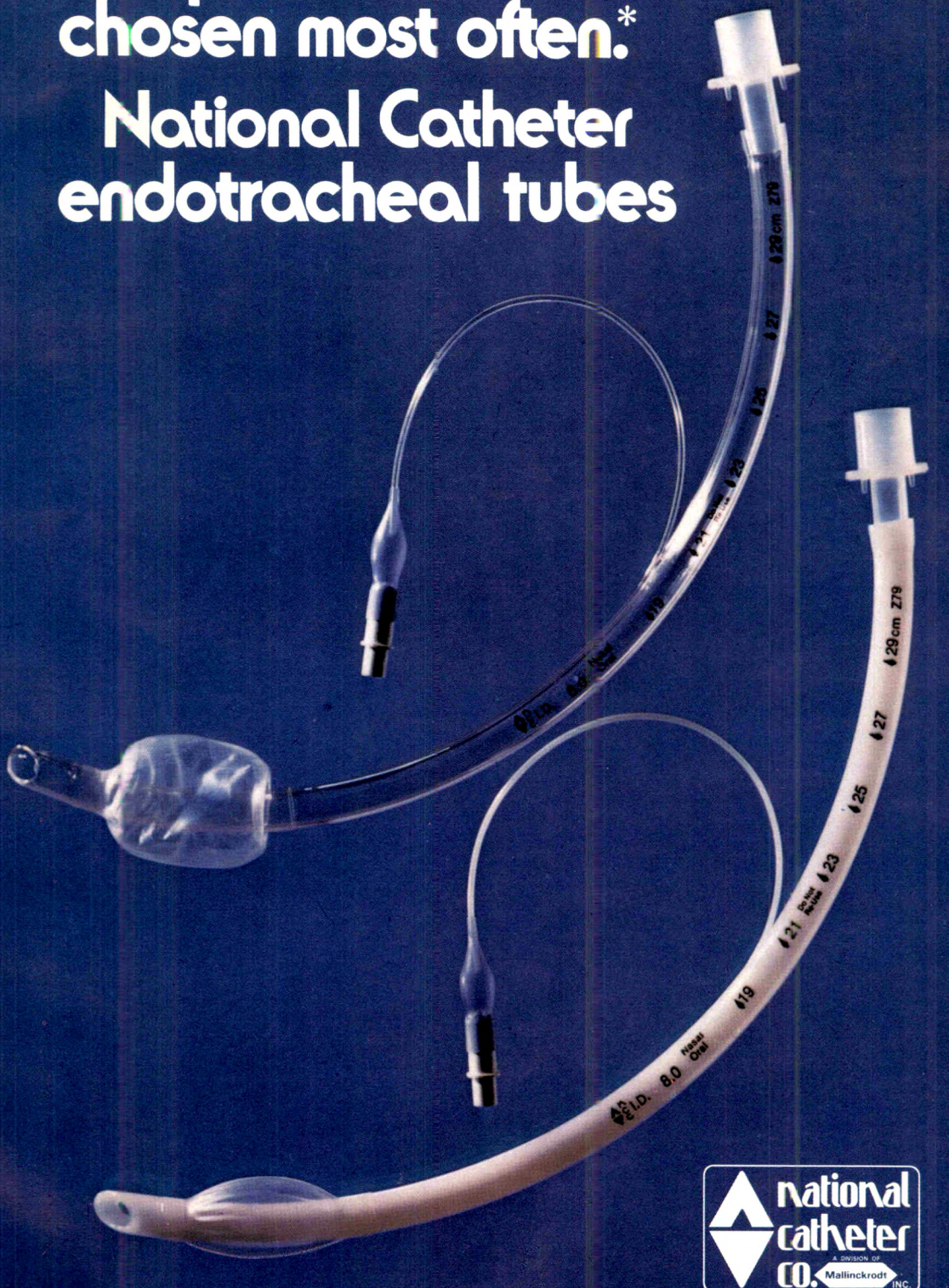
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EDO-050N

May, 1977

The professional standard; chosen most often.*

National Catheter endotracheal tubes



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Home of the Sheridan Line of Catheters • Hook Road, Argyle, New York, 12809 Tel (518) 638-8232

*Source: IMS America Ltd. – Fourth Quarter, 1977

See package insert prior to use.

ANTILIRIUM

(Physostigmine Salicylate)

TO REVERSE THE TOXIC EFFECTS UPON THE CENTRAL NERVOUS SYSTEM CAUSED BY DRUGS IN CLINICAL OR TOXIC DOSAGES CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING.

DRUGS AND CHEMICALS CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING:

- AMITRIPTYLINE (Elavil, Triavil, Etrafon)
- ANISOTROPINE METHYLBROMIDE
- ATROPINE
- BELLADONNA
- BENACTYZINE
- CHLORPHENIRAMINE
- CYCLOPENTOLATE
- DESIPRAMINE (Norpramin, Pertofrane)
- DICYCLOMINE
- DIPHENHYDRAMINE
- DOXEPIN (Sinequan)
- HOMATROPINE
- HYOSCINE
- HYOSCYAMUS
- IMIPRAMINE (Tofranil, Presamine)
- ISOPROPAMIDE
- MEPENZOLATE
- METHANTHELINE
- METHAPYRILENE
- NORTRIPTYLINE (Aventyl)
- PIPENZOLATE BROMIDE (Piptal)
- PROPANTHELINE
- PROTRIPTYLINE (Vivactil)
- PYRILAMINE
- SCOPOLAMINE
- STRAMONIUM
- PHENOTHIAZINES
- TRICYCLIC ANTIDEPRESSANTS (Aventyl, Elavil, Etrafon, Norpramin, Pertofrane, Presamine, Tofranil, Triavil, Vivactil)
- THIORIDAZINE (Mellaril)

INDICATIONS: TO REVERSE THE TOXIC EFFECTS UPON THE CENTRAL NERVOUS SYSTEM CAUSED BY DRUGS IN CLINICAL OR TOXIC DOSAGES CAPABLE OF PRODUCING ANTICHOLINERGIC POISONING.

SEVERE ANTICHOLINERGIC POISONING MAY PRODUCE: COMA, MEDULLARY PARALYSIS AND DEATH.

CENTRAL TOXIC EFFECTS MAY INCLUDE: HALLUCINATIONS, DELIRIUM, DISORIENTATION, ANXIETY AND HYPERACTIVITY.

Before prescribing, please consult complete product information, a summary of which follows:

ACTION: ANTILIRIUM (physostigmine salicylate) is a salicylic acid derivative of an alkaloid extracted from seeds of Physostigma Venenosum (calabar bean). The action of the parasympathetic nerves is intermediated by the formation of acetylcholine at the peripheral end of these nerves. Physostigmine inhibits the destructive action of cholinesterase and thereby prolongs and exaggerates the effect of the acetylcholine.

Physostigmine contains a tertiary amine and easily crosses the blood brain barrier, while neostigmine contains a quaternary amine and is not capable of crossing the structure. This may explain why neostigmine does not cause reversal of anticholinergic-induced delirium while physostigmine does.

Dramatic reversal within minutes of coma, hallucinations, and other signs can be expected if the diagnosis is correct and the patient has not suffered anoxia or other insult. Therapeutic doses may be necessary at intervals as life-threatening signs recur. Physostigmine is destroyed in the body in 60 to 120 minutes.

CONTRAINDICATIONS: Physostigmine should not be used in the presence of asthma, gangrene, diabetes, cardiovascular disease, mechanical obstruction of the intestines or urogenital tract or any vagotonic state, and in patients receiving choline esters or depolarizing neuromuscular blocking agents.

WARNING: If excessive symptoms of salivation, emesis, urination and defecation occur, the use of ANTILIRIUM should be terminated. If excessive sweating or nausea occur, the dosage should be reduced.

Intravenous administration should be at a slow, controlled rate, no more than 1 mg. per minute (see dosage). Rapid administration can cause bradycardia, hypersalivation leading to respiratory difficulties and possibly convulsions.

An overdosage of ANTILIRIUM can cause a cholinergic crisis.

PRECAUTIONS: Because of the possibility of hypersensitivity in an occasional patient, atropine sulfate injection should always be at hand since it is an antagonist and antidote for physostigmine.

ADMINISTRATION AND DOSAGE: The usual adult dose of ANTILIRIUM is 0.5 to 2.0 mg. intramuscularly or intravenously. Intravenous administration should be at a slow, controlled rate of no more than 1 mg. per minute. It may be necessary to repeat dosages of 1 mg. to 4 mg. at intervals as life threatening signs such as arrhythmias, convulsions and deep coma recur.

IN ALL CASES OF POISONING, THE USUAL SUPPORTIVE MEASURES SHOULD BE UNDERTAKEN.

SUPPLIED: 2 ml. ampules containing:
PHYSOSTIGMINE SALICYLATE 1 mg. per ml.
Packed 12 ampules per box.

NDC 0456-1037-12

CAUTION: Federal law prohibits dispensing without prescription.

REFERENCES:

Greene, L. T.: Physostigmine treatment of anticholinergic drug depression in postoperative patients. Anesth & Analg, March-April 1971; 50-2: 222-226.

Rumack, B.: Anticholinergic poisoning: Treatment with physostigmine. Pediatrics, Sept. 1973.

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Selected cases for Ketalar

There are certain situations where the advantages of Ketalar suggest its serious consideration. Four such hypothetical situations are detailed here.
A fifth hypothetical case illustrates a situation in which Ketalar probably should be used only with caution.



Geriatric surgical procedure

Ketalar offers advantages in minor rectal surgery on elderly patients. When properly administered, Ketalar usually does not depress the patient's blood pressure or pulse rate, which can be a distinct advantage with any patient who is likely to develop hypotension. Further, emergence reactions normally are not a problem with patients in the older age group (over 65).



Severely burned patients

Patients with severe burns—and particularly children—are often excellent cases for Ketalar. In children, Ketalar offers rapid surgical anesthesia (generally within three to four minutes) at a range of 9 to 13 mg/kg, with the effect lasting from 12 to 25 minutes (the time intervals are for IM, not IV). Intramuscular administration avoids the possible difficulty in locating the vein in burn patients (particularly helpful in children where the veins are small). IM administration is also convenient and effective for repeated short-term anesthesia for such procedures as changing burn dressings, and skin grafts.

advancement in anesthesiology

Ketalar (Ketamine HCl injection)
Parke-Davis

Brief summary of prescribing information.

SPECIAL NOTE

EMERGENCE REACTIONS HAVE OCCURRED IN APPROXIMATELY 12% OF PATIENTS.

THE PSYCHOLOGICAL MANIFESTATIONS VARY IN SEVERITY BETWEEN PLEASANT, DREAMLIKE STATES, VIVID IMAGERY, HALLUCINATIONS, AND EMERGENCE DELIRIUM. IN SOME CASES, THESE STATES HAVE BEEN ACCOMPANIED BY CONFUSION, EXCITEMENT, AND IRRATIONAL BEHAVIOR WHICH A FEW PATIENTS RECALL AS AN UNPLEASANT EXPERIENCE. THE DURATION ORDINARILY LASTS NO MORE THAN A FEW HOURS; IN A FEW CASES, HOWEVER, RECURRENCES HAVE TAKEN PLACE UP TO 24 HOURS POSTOPERATIVELY. NO RESIDUAL PSYCHOLOGICAL EFFECTS ARE KNOWN TO HAVE RESULTED FROM USE OF KETALAR.

THE INCIDENCE OF THESE EMERGENCE PHENOMENA IS LEAST IN THE YOUNG (15 YEARS OF AGE OR LESS) AND ELDERLY (OVER 65 YEARS OF AGE) PATIENT. ALSO, THEY ARE LESS FREQUENT WHEN THE DRUG IS GIVEN INTRAMUSCULARLY.

THESE REACTIONS MAY BE REDUCED IF VERBAL, TACTILE, AND VISUAL STIMULATION OF THE PATIENT IS MINIMIZED DURING THE RECOVERY PERIOD. THIS DOES NOT PRECLUDE THE MONITORING OF VITAL SIGNS. IN ADDITION, THE USE OF A SMALL HYPNOTIC DOSE OF A SHORT-ACTING OR ULTRASHORT-ACTING BARBITURATE MAY BE REQUIRED TO TERMINATE A SEVERE EMERGENCE REACTION. THE INCIDENCE OF EMERGENCE REACTIONS IS REDUCED AS EXPERIENCE WITH THE DRUG IS GAINED.

WHEN KETALAR IS USED ON AN OUTPATIENT BASIS, THE PATIENT SHOULD NOT BE RELEASED UNTIL RECOVERY FROM ANESTHESIA IS COMPLETE AND THEN SHOULD BE ACCOMPANIED BY A RESPONSIBLE ADULT.

INDICATIONS

Ketalar (ketamine HCl injection) is recommended:

1. as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation. Ketalar is best suited for short procedures but it can be used, with additional doses, for longer procedures;

2. for the induction of anesthesia prior to the administration of other general anesthetic agents;

3. to supplement low-potency agents, such as nitrous oxide.

CONTRAINDICATIONS

Ketamine hydrochloride is contraindicated in those in whom a significant elevation of blood pressure would constitute a serious hazard and those who have shown hypersensitivity to the drug.

WARNINGS

1. Ketalar should be used by or under the direction of physicians experienced in administering general anesthetics and in maintenance of an airway and in the control of respiration.

2. Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.

3. Barbiturates and Ketalar, being chemically incompatible because of precipitate formation, *should not* be injected from the same syringe.

4. Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketalar.

5. Postoperative confusional states may occur during the recovery period.

6. Respiratory depression may occur with overdosage or too rapid a rate of administration of Ketalar, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

Usage in Pregnancy

Since the safe use in pregnancy, including obstetrics (either vaginal or abdominal delivery), has not been established, such use is not recommended.

PRECAUTIONS

1. Because pharyngeal and laryngeal reflexes are usually active, Ketalar (ketamine HCl injection) should not be used alone in surgery or diagnostic procedures of the pharynx, larynx, or bronchial tree. Mechanical stimulation of the pharynx should be avoided, whenever possible, if Ketalar is used alone. Muscle relaxants, with proper attention to respiration, may be required in both of these instances.

2. Resuscitative equipment should be ready for use.

3. ***The incidence of emergence reactions may be reduced*** if verbal and tactile stimulation of the patient is minimized during the recovery period. This does not preclude the monitoring of vital signs (see Special Note).

4. The intravenous dose should be administered over a period of 60 seconds. More rapid administration may result in respiratory depression or apnea and enhanced pressor response.

5. In surgical procedures involving visceral pain pathways, Ketalar should be supplemented with an agent which obtunds visceral pain.

6. Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient.

7. An increase in cerebrospinal fluid pressure has been reported following administration of ketamine hydrochloride. Use with extreme caution in patients with preanesthetic elevated cerebrospinal fluid pressure.

ADVERSE REACTIONS

Cardiovascular: Blood pressure and pulse rate are frequently elevated following administration of Ketalar. However, hypotension

(ketamine HCl inj) . . . and a caution



Manipulative diagnostic procedure

Ketalar facilitates diagnostic procedures in which the patient must be moved freely, and in which the maintenance of unaided respiration is essential. The pneumoencephalogram is an example. Once anesthesia is established, the patient can be transferred from a supine to an upright, supported position with ease since Ketalar maintains adequate unaided respiration, and there is minimal relaxation of the skeletal muscles.



Emergency room treatment

A good case for Ketalar can be made for use in accident victims with unknown medical histories brought to the emergency room. In the absence of positive medical history, Ketalar can be a useful agent because of its wide margin of safety. Consideration should be given to the effects of a significant increase in blood pressure, hypersensitivity to the drug, and an elevation in cerebrospinal fluid pressure. Ketalar also provides the benefit of rapid onset, and decreases the chance of aspiration because of active laryngeal-pharyngeal reflexes.



A caution:

Caution should be exercised when administering Ketalar to patients who are known to be alcoholics or who are acutely alcohol-intoxicated as such patients may be prone to untoward reactions.

---

d bradycardia have been observed. rhythmia has also occurred.

spiration: Although respiration is frently stimulated, severe depression of piration or apnea may occur following id intravenous administration of high ses of Ketalar (ketamine HCl injection). yngospasms and other forms of airway struction have occurred during Ketalar esthesia.

: Diplopia and nystagmus have been ed following Ketalar administration. It o may cause a slight elevation in intraular pressure measurement.

rchological: (See Special Note).

urological: In some patients, enhanced letal muscle tone may be manifested by ic and clonic movements sometimes embling seizures (see Dosage and ministration).

strointestinal: Anorexia, nausea and miting have been observed; however this ot usually severe and allows the great jority of patients to take liquids by mouth rtly after regaining consciousness e Dosage and Administration).

neral: Local pain and exanthema at the ection site have infrequently been reted. Transient erythema and/or morbilim rash have also been reported.

SAGE AND ADMINISTRATION

operative Preparations:

While vomiting has been reported following talar administration, airway protection is ually afforded because of active laryngeal-aryngeal reflexes. However, since these exes may also be diminished by supplentary anesthetics or muscle relaxants, the ssibility of aspiration must be considered. talar is recommended for use in the ient whose stomach is not empty when, in judgment of the practitioner, the benefits the drug outweigh the possible risks.

Atropine, scopolamine, or other drying ent should be given at an appropriate erval prior to induction.

Dosage

As with other general anesthetic agents, the individual response to Ketalar (ketamine HCl injection) is somewhat varied depending on the dose, route of administration, and age of patient, so that dosage recommendation cannot be absolutely fixed. The drug should be titrated against the patient's requirements.

Onset and Duration:

Because of rapid induction following the initial intravenous injection, the patient should be in a supported position during administration.

The onset of action of Ketalar (ketamine HCl injection) is rapid; an intravenous dose of 2 mg/kg (1 mg/lb) of body weight usually produces surgical anesthesia within 30 seconds after injection, with the anesthetic effect usually lasting five to ten minutes. If a longer effect is desired, additional increments can be administered intravenously or intramuscularly to maintain anesthesia without producing significant cumulative effects.

Intramuscular doses, from experience primarily in children, in a range of 9 to 13 mg/kg (4 to 6 mg/lb) usually produce surgical anesthesia within three to four minutes following injection, with the anesthetic effect usually lasting 12 to 25 minutes.

Induction:

Intravenous Route: The initial dose of Ketalar administered intravenously may range from 1 mg/kg to 4.5 mg/kg (0.5 to 2 mg/lb). The average amount required to produce five to ten minutes of surgical anesthesia has been 2 mg/kg (1 mg/lb).

NOTE: The 100 mg/ml concentration (S-V 1585) of Ketalar, *should not* be injected intravenously without proper dilution. It is recommended the drug be diluted with an equal volume of either Sterile Water for Injection, USP, Normal Saline, or 5% Dextrose in Water.

Rate of Administration: It is recommended that Ketalar be administered slowly (over a period of 60 seconds). More rapid administration may result in respiratory depression and enhanced pressor response.

Intramuscular Route: The initial dose of Ketalar administered intramuscularly may range from 6.5 to 13 mg/kg (3 to 6 mg/lb). A dose of 10 mg/kg (5 mg/lb) will usually produce 12 to 25 minutes of surgical anesthesia.

Maintenance of Anesthesia:

Increments of one half to the full induction dose may be repeated as needed for maintenance of anesthesia. However, it should be noted that purposeless and tonic-clonic movements of extremities may occur during the course of anesthesia. These movements do not imply a light plane and are not indicative of the need for additional doses of the anesthetic.

It should be recognized that the larger the total dose of Ketalar (ketamine HCl injection) administered, the longer will be the time to complete recovery.

Supplementary Agents:

Ketalar is clinically compatible with the commonly used general and local anesthetic agents when an adequate respiratory exchange is maintained.

HOW SUPPLIED

Ketalar is supplied as the hydrochloride in concentrations equivalent to ketamine base.

N 0071-4581-15—Each 50-ml vial contains 10 mg/ml. Supplied in cartons of 10.

N 0071-4581-12—Each 20-ml vial contains 10 mg/ml. Supplied in cartons of 10.

N 0071-4582-10—Each 10-ml vial contains 50 mg/ml. Supplied in cartons of 10.

N 0071-4585-03—Each 5-ml vial contains 100 mg/ml. Supplied in cartons of 10. **SG**

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Anesth Analg
Vol. 57 Nov.-Dec., 1978

Editorial

A New Look For Our Journal

The Journal you are now reading is the last you will receive in its present style. Beginning with the January-February 1979 issue of Volume 58, it will be cosmetically "born again". First of all, the name of the Journal will be shortened to "Anesthesia and Analgesia"—eliminating the Current Researches portion which has been a part of its name from the outset. The old familiar English script will be retired in favor of a more modern type style. At the same time, the size will be increased to 8½″ × 11″ to conform to the almost universal trend in medical publications. The yellow cover (a virtual trademark) will be retained but with a discreet streak or two of henna to complete the general facelift.

At age 58, the Journal can look back at an interesting and colorful history as it inched upward and outward to remarkably parallel the growth of the specialty.

It started a mite surreptitiously in 1914 as a Quarterly Supplement to the American Journal of Surgery. After 8 years as a "piggy back", it jumped off on its own in 1922 as a full-fledged, albeit modest, 6″ × 9″ publication titled "Current Researches in Anesthesia and Analgesia." Because anesthetists were so few in number and spread all over the world, "Current Researches", as the sole journal in anesthesia, rapidly became a repository for virtually everything they wrote on the subject. A folksy/formal type publication evolved to serve this close-knit band of pioneers. This international flavor was maintained to some extent until World War II. Thereafter, as increasing numbers of anesthesia societies spawned more anesthesia journals, the need for a catalyst publication ceased, and Current Researches assumed the journalistic role it retains to this day: an independent, apolitic, largely North American, clinically oriented journal.

In 1957 as anesthesiology achieved specialty status, the face of Current Researches was dramatically changed to mirror the exuberant "coming of age" era. Its name was re-arranged to become "Anesthesia and Analgesia . . . Current Researches (thus putting the horse before the cart where it properly belongs). It increased its size to 7″ × 10″ and burst forth in a bold yellow cover.

Specialty recognition achieved, it settled back to enjoy and expand its role as purveyor of everything anybody needed to know about anesthesiology, and then some. Meantime, as the specialty grew, so too did the literature and busy practitioners could no longer keep up with the volume of reading material. This Journal responded again—this time by sharpening its editorial eyes and scissors and eliminating some of the frills and features. A leaner and meatier journal resulted.

Whether or not our impending changes foretell or coincide with a new and expanding era for the specialty, time will tell. We know the Journal will be bigger—we also feel it will be better. One thing is certain: we remain committed to publishing a journal primarily for the practicing anesthesiologist. At the same time, we recognize that each year we address more of you who are knowledgeable and articulate in the basic sciences and who find the "why's" of research not only interesting but essential to the effective implementation of the practical "how to's".

It is rare, indeed, that we use our Journal pages to talk about ourselves—the last time being in 1971 when we observed our 50th anniversary. We thought it appropriate this time to alert you to the new Anesthesia and Analgesia you will receive in 1979. In doing so, we could not resist the opportunity to reflect a little on the past as it relates to the current chapter we are closing and the next one to come.

Emerson A. Moffitt, M.D.
Chairman of the Board
International Anesthesia
Research Society

Nicholas M. Greene, M.D.
Editor in Chief

Editorial

Pharmacokinetics: The Scientific Basis for Drug Selection

In this issue of the journal Hug reviews the principles of pharmacokinetics with special emphasis on IV administered drugs. While the uptake, distribution, and elimination of inhalation anesthetics have been well studied, the fate of IV drugs has received somewhat less attention. Since both the therapeutic and the toxic effects of most drugs depend upon their concentrations at the active sites, it is important for the anesthesiologist to understand and apply the principles of pharmacokinetics to ensure that the delicate balance between therapeutic effectiveness and toxic manifestations is achieved. Pharmacokinetics may be defined as the quantitative study of drug absorption, distribution, biotransformation, and elimination from the body. Knowledge of pharmacokinetics will aid the clinician in selection of a specific drug and will suggest dosage routes and schedules which should help to produce a rapid and controllable effect with minimal potential for drug toxicity. A full understanding of pharmacokinetics requires knowledge not only of the chemistry of the drug itself, but also an understanding of drug metabolism and organ function. With regard to the chemistry of the compounds, the principles of solubility, of protein binding, and of ionization (as well as many others) influence drug selection. An understanding of organ physiology is essential since drug choice and dosage schedules depend upon body composition, the state of the circulatory system, and hepatic and renal function. While any number of examples might illustrate these principles, the following serve to demonstrate that both chemistry and human physiology influence drug therapy.

Recent work by Scanlon and coworkers revealed that infants born of mothers who received continuous lumbar epidural anesthesia with bupivacaine demonstrated no significant neurobehavioral abnormalities, while those delivered of mothers who received a similar anesthetic with lidocaine or mepivacaine demonstrated depressed neurobehavioral responses postpartum.[1] Comparison of the fetal to maternal concentration ratios among the three drugs revealed that the greatest ratio occurred with mepivacaine, an intermediate value was found with lidocaine, and the ratio was least with bupivacaine—results which were consistent with the neurobehavioral responses of the infants. While numerous factors may account for these findings, at least two characteristics which relate to the physical properties of the local anesthetics may help explain the results. First, Tucker and coworkers demonstrated significant differences in the binding characteristics of these drugs in maternal and fetal plasma.[2] Bupivacaine was found to have a great affinity for maternal plasma proteins, while lidocaine was less strongly bound to maternal plasma. Also, fetal blood concentrations of local anesthetics were influenced by the lipid solubilities of the local anesthetics, since those drugs which were more lipid soluble were cleared more rapidly from the blood stream. Bupivacaine is far more liquid soluble than either mepivacaine or lidocaine. This may account in part for the observation that, following epidural anesthesia in the mothers, the halflife of mepivacaine was approximately 9 hours in the newborn, while the corresponding value for lidocaine was approximately 3 hours and the halflife of bupivacaine could not be determined since it was not detectable in the fetal blood except in one infant. Overall, then, both the neurobehavioral testing and the data on maternal and fetal blood concentrations suggest that the clinical properties of local anesthetics, especially protein binding and lipid solubility, may have important consequences for the newborn in the early postpartum period.

A second example which demonstrates the importance of altered physiology on drug kinetics is illustrated by the use of muscle

relaxants in patients with renal failure. Churchill-Davidson[3] and coworkers administered either d-tubocurarine or gallamine to patients who were functionally anepheric. They monitored neuromuscular transmission during and after operation and carefully documented the degree of depression produced by either gallamine or d-tubocurarine. Of the 6 patients who received d-tubocurarine, all demonstrated a normal recovery of neuromuscular transmission and, following the administration of an anticholinesterase agent, no residual paresis was observed. In contrast, 3 of the 5 patients who received gallamine remained partially or completely paralyzed for up to 48 hours thereafter. Again, the results are predictable in light of our present understanding of the routes of metabolism and elimination of the muscle relaxants. Gallamine is eliminated by renal excretion and, in the absence of renal function, the effect of the drug persists for several days. In contrast to gallamine, d-tubocurarine may be eliminated from the body by another route when renal excretion is inadequate. Cohen and coworkers observed the elimination of d-tubocurarine from dogs which were rendered anephric by ligation of the renal pedicle.[4] In the intact dog approximately 75% of the administered d-tubocurarine was recovered in the urine within 24 hours and an additional 10% was found in the bile. In the absence of renal function, the biliary route for excretion was greatly enhanced and the drug continued to be cleared from the plasma, although at a slightly slower rate than in the animal with normal renal function.

The maturity of anesthesiology as a discipline can be estimated by its advancement from primarily a phenomenological specialty (ie, one based primarily on clinical experience or case reports) toward a clinical science firmly grounded on the principles of physiology, pathophysiology, and pharmacology. If we are to continue to gain the respect of our colleagues both as clinicians and clinical scientists, it is essential that we unite a clear understanding of body function with an equally firm understanding of drug action in order to yield the optimum prescription of anesthetic care for each patient. While the basic principles of physiology seem well established, the emerging explosion of information in the area of pharmacokinetics will require much effort if we are to grasp this important aspect of our practice. While such efforts are both arduous and time consuming, the end result is certain to result in better patient care and to enhance the emergence of anesthesiology as a clinical science.

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Anesth Analg
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Hepatocyte Responses to Volatile Anesthetics: Changes in Surface Scanning and Enzyme Leakage

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The effects of volatile anesthetics were assessed in freshly isolated rat hepatocytes by surface-scanning electron microscopy and by measuring leakage of cellular enzymes, lactate dehydrogenase and β-glucuronidase into the surrounding medium. The order of potency in regard to their capacity to produce alterations of these parameters was halothane = methoxyflurane > ether = control. The extent of enzyme leakage from hepatocytes exposed to halothane or methoxyflurane was both dose dependent and, for the first 30 minutes, time dependent. Surface scanning of the isolated hepatocytes showed that both halothane and methoxyflurane produced enzyme leakage and morphologic changes in cellular membranes, but ether did not. These studies demonstrate that scanning electron microscopy and enzyme leakage from cells are useful for the evaluation of drug-induced changes in lever cells in vitro. The relation between these drug-induced changes and clinical hepatotoxicity remains to be elucidated.

Key Words—LIVER, hepatotoxicity. TOXICITY, hepatic. ANESTHETICS, volatile, ether. ANESTHETICS, volatile, halothane. ANESTHETICS, volatile, methoxyflurane.

THERE is general agreement regarding the usefulness of the halogenated hydrocarbon anesthetics in clinical practice because of their controllable, potent, nonexplosive, and nonflammable characteristics. There is a great deal of controversy about the mechanism and incidence of hepatotoxicity in patients exposed to halogenated anesthetics. Much of it results from the fact that the hepatotoxic potential of these drugs in experimental animals cannot necessarily be extrapolated to that in man. Evaluation of the hepatotoxicity of these agents in man is also hampered by its low incidence and the difficulty of evaluation of the etiology of hepatic dysfunction in postoperative patients.

Previous work in this laboratory demonstrated a positive correlation between the cytotoxicity in vitro and the clinical hepatotoxic potential in vivo for phenothiazines,[1] erythromycin derivatives,[2,3] and a laxative preparation.[4] The present investigation was undertaken to compare the type and extent of changes induced in isolated rat hepatocytes by means of scanning electron microscopy and leakage of intracellular enzymes

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after exposure to three volatile anesthetics—ethyl ether* (E), halothane* (H), and methoxyflurane* (MF)—on the basis that such changes may throw light on the mechanism of possible clinical hepatotoxicity.

MATERIALS AND METHODS

Isolation of Rat Liver Cells—Hepatocytes were isolated from the livers of male Sprague-Dawley rats (220 to 250 g) which had free access to the standard pellet diet and water until they were anesthetized with ether prior to liver perfusion. Isolated hepatic cells were prepared by the method of Berry and Friend,[5] as modified by Seglen.[6] After collagenase (Worthington Biochemical Corp., Freehold, NJ) perfusion, the isolated hepatocytes were suspended in Hanks' Balanced Salt Solution, pH 7.2 (Grand Island Biological Company, Grand Island, NY). Membrane integrity and viability of cells were determined by O_2 consumption before and after exposure to succinate as described by Baur et al,[7] and by trypan blue exclusion; suspensions with 92 ± 5.0% viable cells were utilized promptly in the experiments.

Drug Cytotoxicity—One million cells suspended in 1 ml of Hanks' Balanced Salt Solution were added to each glass screwcap (16 x 125 mm) tube containing 7 ml of Hanks' Balanced Salt Solution. The amount of drug necessary to achieve the proper concentration was introduced in the cell suspension medium and the tubes were capped tightly, mixed gently, and incubated horizontally at 37 C in the air contained in the tube. Controls were treated identically except that no drugs were added to the medium. At the end of incubation (10 to 60 min), the medium was withdrawn after a brief centrifugation (50 x g for 2 min) and immediately assayed for enzyme activity. Lactate dehydrogenase (LDH) was assayed by the method of Wroblewski and LaDue[8] and β-glucuronidase (BG) by the method of Greenberg.[9]

Scanning Electron Microscopy—After exposure to a medium containing no drug (controls) or one of the drugs in solution, the cells were layered on coverslips which had been previously treated with 1% poly L-lysine. The cells were then fixed with 2% isotonic glutaraldehyde buffered with 0.2 M phosphate buffer, pH 7.2, for 24 hr at 4 C. Fixed samples were dehydrated in graded series of ethanol (30, 70, 95, and 100% v/v) for 5 min each, followed by exposure to freon 113. The samples were transferred to the critical point apparatus (OMAR SPC 1500) and ethanol was replaced by freon 13 (bp 29 C, psi 560). The slides were then coated with gold in a Technics Hummer apparatus. Specimens were examined and photographed in a JEOL-JSM-35 scanning electron microscope using an accelerating voltage of 25 kV and a tilt of 45°.

Statistical Analysis—The data presented in this report are means and standard errors of the results of 4 different preparations for each experiment. Each experiment was repeated at least twice. The data were analyzed by Student's *t*-test. A difference was considered "significant" when a $p<0.01$ was obtained.

RESULTS

Cytotoxicity Experiments — The leakage of LDH (a cytoplasmic enzyme) and BG (a lysosomal enzyme) from the hepatocytes into the surrounding medium was used to quantitate the effects of general anesthetics on membrane integrity of hepatocytes. The leakage of LDH was expressed as units of enzyme per millilitre of incubation medium, and BG as micrograms of β-naphthol which was freed by the enzyme, per millilitre of incubation medium. The comparative effects of E, H, or MF at 60 min are shown in fig 1. At the level of 1.5 L of drugs per millilitre medium, ether caused no greater enzyme leakage than controls. In contrast, both MF and H produced effects significantly greater than control or ether. After 30 and 60 min of incubation, the enzyme leakage was the same, suggesting that maximum

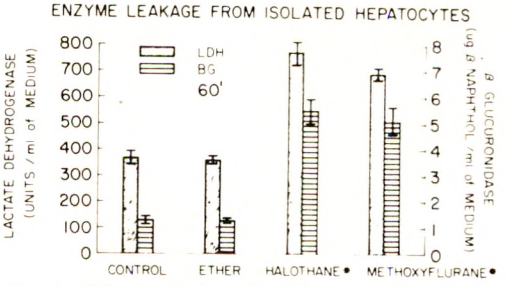


FIG 1. Effects of ether, halothane, and methoxyflurane on isolated rat hepatocytes as measured by the leakage of lactate dehydrogenase and β-glucuronidase into the medium. The cells were incubated with the drugs (1.5 μL/ml) for 1 hr at 37 C.

*Halothane and methoxyflurane differ significantly from control and ether ($p<0.01$).

*Ethyl ether, halothane, and methoxyflurane were obtained from Mallinckrodt, Inc. (St. Louis, MO), Ayerst Laboratories, Inc. (New York, NY), and Abbott Laboratories (Chicago, IL), respectively.

drug effect had been achieved during 30 min of exposure. The results of exposing the cells for 60 min to different concentrations of H and MF (0.5, 1.0, and 1.5 μL/ml) are shown in fig 2. There was an increase in enzyme leakage after increasing the drug level in the media, except that the enzyme leakage at 1 μL/ml did not differ significantly from that at 1.5 μL/ml. Figure 3 shows that as early as 10 min after incubation, both H and MF caused statistically significant leakage of enzymes (LDH, BG) above the control, and the enzyme leakage increased steadily up to 30 min of incubation. Previous experiments have been performed measuring the concentration of drug after the solution was prepared.[10] Under identical experimental conditions a solution of 1.0 μL/ml of E, H, or MF contains 829, 499, and 478 μg/ml respectively.

Morphological Changes — Morphological changes by surface scanning electron microscopy corroborated the results of the enzyme leakage and demonstrated a direct effect of the drugs on plasma membranes. Hepatocytes exposed to control medium appeared spherical, with plasma membranes covered with numerous microvilli (fig 4A and 5A). After 1 hr incubation in medium containing one of the drugs at a concentration of 1.5 μL/ml of medium, the appearance of gross changes in cell morphology was drug dependent. Cells exposed to ether (fig 4B and 5B) were slightly enlarged and some of the microvilli became swollen, assuming a bullaelike appearance; however, no other changes occurred on the cell membrane. In contrast, cells treated with H or MF became distorted in shape and swollen, the microvilli disappeared, and the surface was grossly eroded (fig 4C, D and 5C, D).

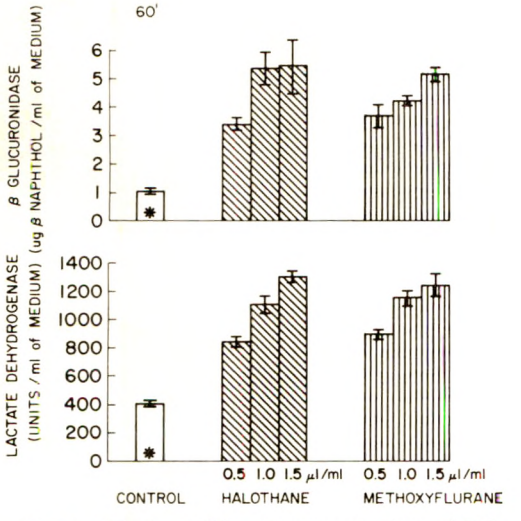


FIG 2. Effects of different concentrations of halothane and methoxyflurane on isolated rat hepatocytes measured by leakage of lactate dehydrogenase and β-glucuronidase into the medium. The cells were incubated with the drugs for 1 hr at 37 C.

*Halothane and methoxyflurane differ significantly from control ($p<0.01$).

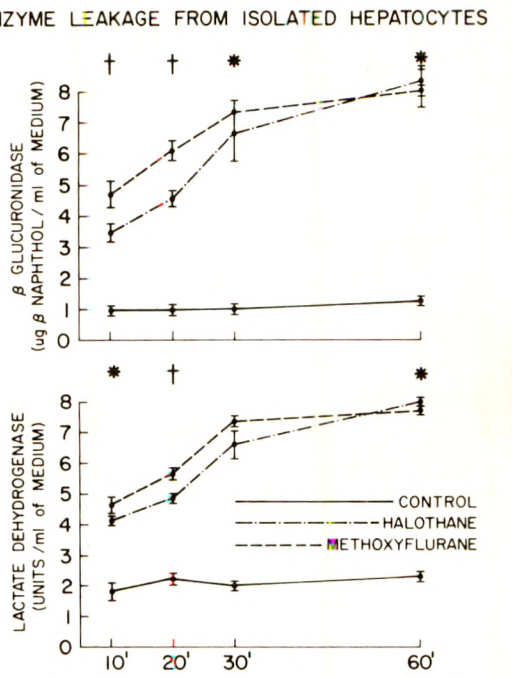


FIG 3. Effects of halothane and methoxyflurane on isolated rat hepatocytes as measured by the leakage of lactate dehydrogenase and β-glucuronidase into the medium. The cells were incubated with the drugs (1.5 μL/ml) for different incubation times at 37 C.

*All drugs are different from control ($p<0.01$).

†Halothane, methoxyflurane, and control differ significantly from each other ($p<0.01$).

DISCUSSION

Marked differences in responses of isolated rat hepatocytes to E, H, and MF have been demonstrated in this study. Ether exerted negligible effects, a finding in agreement with the fact that ether has not been found to be hepatotoxic in man.[11] In contrast, the surfaces of the plasma membrane of isolated rat liver cells were significantly affected by H and MF. The concentrations of the anesthetics in the medium used in our experiments correspond to the anesthetic concentrations reported in blood taken from the hepatic vein of experimental animals during anesthesia.[12]

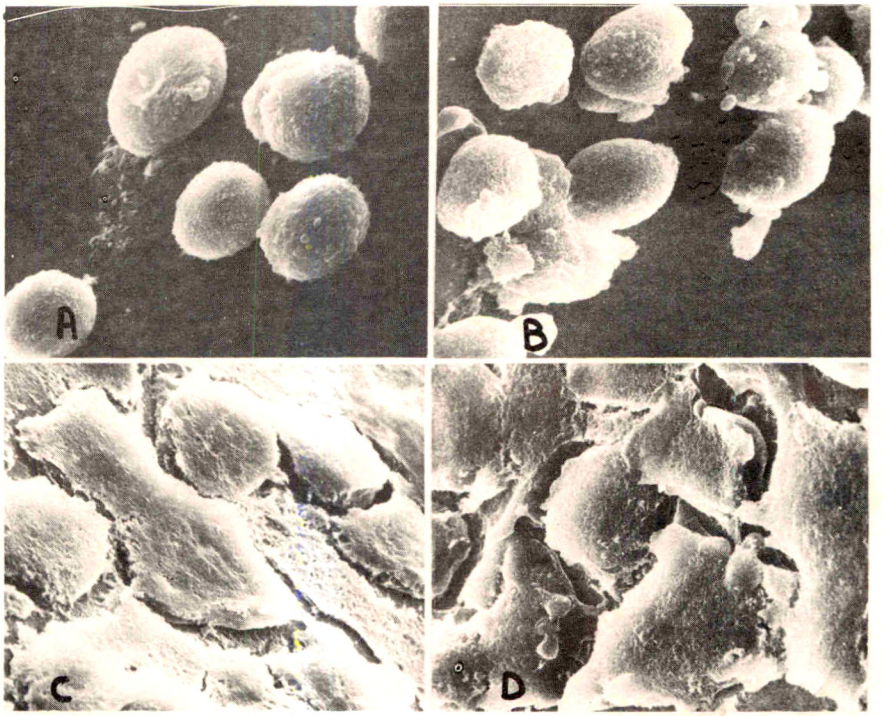


FIG 4. Morphological appearance of isolated rat hepatocytes under scanning electron microscopy after the cells were exposed for 1 hr at 37 C to medium without drugs (A) or with ether (B), halothane (C), or methoxyflurane (D) at 1.5 μL/ml (original magnification × 1500)

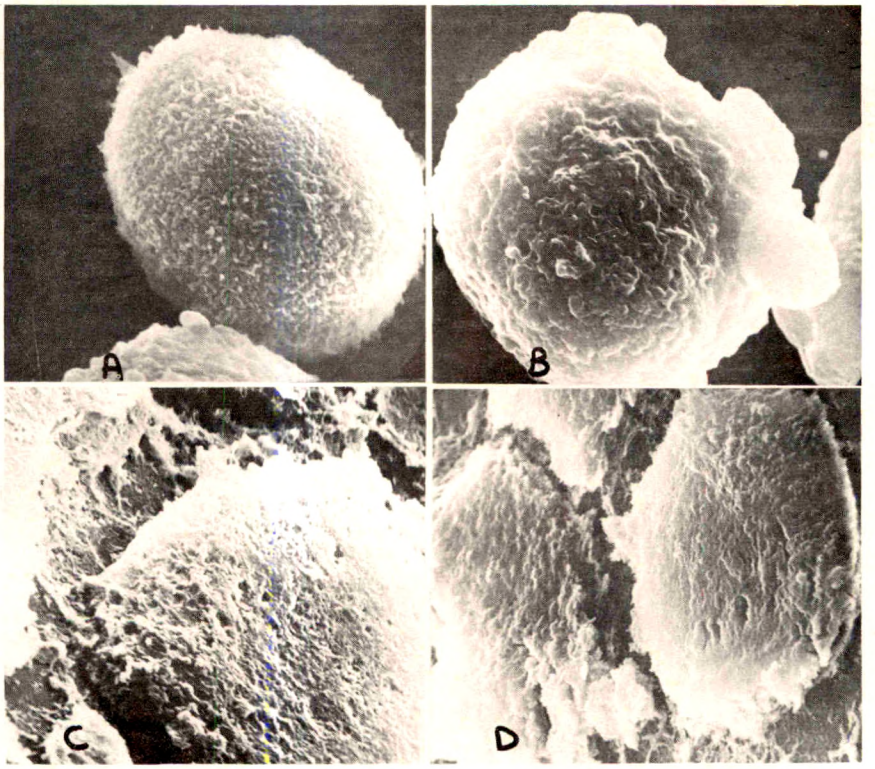


FIG 5. Rat hepatocytes treated the same as in fig 4 except original magnification × 7200: medium without drugs (A), ether (B), halothane (C), methoxyflurane (D).

The available clinical and pathological data suggest that H and MF can occasionally produce hepatic necrosis in man.[11-13] The mechanism of MF or H hepatotoxicity is not known and the incidence is very low, probably less than 1 in 10,000 exposures. Allergic or hypersensitivity mechanisms have been postulated by some and rejected by others.[14-16] This laboratory has reported data demonstrating a correlation between in vitro cytotoxic potential and in vivo incidence of hepatotoxicity for other therapeutic drugs such as phenothiazines, erythromycin, and oxiphenisatin.[1,2,4] Moreover, cytotoxic effects of these anesthetics were demonstrated on a cell line of rat liver hepatoma[17] and in Chang liver-cell cultures.[10] Results of earlier reports[10,17-20] suggested that these halogenated anesthetics can exert a direct effect on cellular membranes, and the present findings on surface scanning support that contention.

The results of the described experiments reveal morphological and permeability alterations on liver-cell plasma membranes which were greater with two volatile anesthetics reported to have hepatotoxic potential in man than were the effects of an anesthetic devoid of hepatotoxic potential in man. The present results, though inadequate to prove that H and MF are clinically hepatotoxic, provide additional knowledge concerning cellular responses to anesthetics which may prove of value in our understanding of events which occur in those rare instances in which H and MF appear to be associated with hepatotoxicity.

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Ventilatory and Cardiovascular Effects of Enflurane Anesthesia During Spontaneous Ventilation in Man

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We examined the cardiovascular and respiratory responses to enflurane-oxygen anesthesia in 12 unpremedicated volunteers during the 2nd and 7th hours of continuous anesthesia without surgery. During the 2nd hour, spontaneous ventilation at 1 MAC (1.86% end-tidal) enflurane produced a marked reduction of tidal volume with a mean $Paco_2$ of 61 torr. Hypercapnia produced cardiovascular stimulation. Cardiac output (CO) increased 31% above the awake control value due to a 41% increase in heart rate (HR). Stroke volume and central venous pressure were unchanged. Systemic vascular resistance fell 52% and mean arterial pressure decreased 38%. Increasing the enflurane concentration to 1.5 MAC accentuated the respiratory depression as the mean $Paco_2$ rose to 76 torr with further increases in CO and HR. Attempts to study cardiovascular responses at 2 MAC were thwarted by apnea.

These results differ from results obtained during controlled ventilation and normal $Paco_2$ in the same subjects. When ventilation is controlled, all cardiovascular variables show a concentration-related depression.

Seven hours of continuous anesthesia produced a significant reversal of the depression of tidal volume. $Paco_2$ was 46, 56, and 67 torr at 1, 1.5, and, for the first time, 2 MAC. The only significant changes in cardiovascular function from the 2nd hour at 1 MAC were increases in HR and left ventricular work. Deepening anesthesia did not produce further significant changes except for greater depression of the Bcg IJ wave and aortic dP/dt at 1.5 MAC.

We conclude that adaptation to the respiratory depression of enflurane occurs over time, although the circulatory adaptation is apparently masked during spontaneous ventilation. With most inhalation anesthetics, including enflurane during controlled ventilation, the circulatory system gradually shows reversal of the initial depressant effects, or even an increase above control values. The fact that this phenomenon is not seen during spontaneous ventilation with enflurane may be due to the decreased sympathetic stimulation caused by the drop in $Paco_2$ which occurs as a function of time during enflurane anesthesia.

Key Words—ANESTHETIC, volatile, enflurane. VENTILATION, carbon dioxide. HEART, cardiac output, myocardial function. BLOOD PRESSURE, systemic vascular resistance.

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ENFLURANE causes a respiratory depression of considerable consequence, as do halothane and isoflurane.[1-5] However, since the exact relationship between ventilatory depression and enflurane concentration has not been measured previously in man, comparison with these other anesthetics has not been possible.

With halothane[3] or isoflurane[6] anesthesia, cardiac output (CO), stroke volume (SV), heart rate (HR), and several indices of myocardial performances are greater during spontaneous ventilation than during controlled ventilation.

To determine the influence of enflurane on ventilation, and the influence of the consequent ventilatory depression on the circulation, we subjected volunteers to periods of spontaneous ventilation during continuous enflurane anesthesia without surgery. Enflurane produced severe ventilatory depression at light and moderate levels of anesthesia, with a resultant marked stimulation of the cardiovascular system.

METHODS

We studied 12, unpremedicated, fasting male subjects 22.5 ± 0.5 SEM years of age. The Human Research Committees of the University of California and the Veterans Administration Hospital, San Diego, approved the study. We obtained informed consent from each volunteer after 2 interviews and a thorough review of the protocol. Volunteers were accepted when their medical history, physical examination, and laboratory studies demonstrated superior health.

These studies were performed in a large room equipped with resuscitation equipment. We warmed the room to maintain the subject's normal body temperature during anesthesia.

The subjects were prepared for the study by technics reviewed in detail in communications.[1-4,6] Arterial, central venous, and peripheral venous pressures were measured directly with Statham transducers, with mean pressures obtained by electronic damping. Cardiac output was determined by the dye-dilution technic. We calculated cardiac cycle intervals from the ECG, arterial pressure wave, and phonocardiograph recordings. We measured forearm (muscle) and finger (skin) blood flow with Whitney mercury-in-Silastic gauges. Oral (awake) and esophageal (anesthetized) temperatures and skin temperatures were obtained with Yellow Springs thermistor probes.

The subjects rested on an ultra-low-frequency air-bearing ballistocardiograph bed weighing 3 kg, undamped, with a natural frequency of 0.18 Hz. Acceleration was transduced in the head-foot (y) axis with a piezoresistive accelerometer. During anesthesia, an air mattress under the subject was inflated periodically and the subject passively exercised to relieve pressure under bony prominences.

When the subject was acclimated to the study environment, as evidenced by normal pulse and blood pressure, a nose clip was applied, and the subject breathed 100% O_2 through a mouthpiece connected to a conventional anesthesia circle system. After allowing 15 minutes for denitrogenation, we obtained duplicate control measurements of arterial blood gases and pH, tidal volume, expired minute ventilation, and respiratory rate. The O_2 electrode was calibrated in the high range of O_2 tension. Base excess was derived by a previously described method.[7] Tidal volume and expired minute ventilation were measured with a Wright respirometer.

Following a rest period, we induced anesthesia with enflurane and O_2 and subsequently inserted a cuffed endotracheal tube. Three subjects required 40 mg of succinylcholine to facilitate intubation. End-tidal (alveolar) enflurane and CO_2 values were obtained via catheters placed in the endotracheal tube for continuous analysis of expired gas by Beckman LB-2 analyzers whose output was displayed on the multichannel recorders employed for cardiovascular measurements. The concentration of enflurane was adjusted to 1 MAC, which is 1.86% in this age group.* During the ensuing hour, we made the above cardiovascular measurements with ventilation controlled to provide eucapnia at 1 and 1.5 MAC (2.79% end-tidal enflurane). Details of these studies are reported in an accompanying article.[10]

After 1 hour of anesthesia, the end-tidal concentration was reduced to 1 MAC. We

*The minimum alveolar concentration (MAC) required to eliminate movement in response to a surgical incision in 50% of patients varies with age.[8] Gion and Saidman's[9] MAC of enflurane was 1.68% for patients whose mean age was 39 years. We estimate a value of 1.86% in 20-to-30-year-old adults.

TABLE 1

Data from the Awake (Control) Period (Mean ± SEM)

Age	22.5	± 0.5 years
Height	179.3	± 1.3 cm
Weight	74.7	± 2.8 kg
Cardiac output	5.36	± 0.12 L/min
Heart rate	62.0	± 1 beats/min
Stroke volume	86.6	± 1.5 ml
Mean right atrial pressure	5.0	± 0.4 torr
Mean arterial pressure	94.0	± 1.0 torr
Systemic vascular resistance	1365.0	± 39.0 ohms
Left ventricular minute work	6.78	± 0.5 joules
Left ventricular stroke work	0.1095	± 0.0 joules
Left ventricular stroke power	0.369	± 0.01 watts
Mean rate of left ventricular ejection	0.292	± 0.01 ml/sec
Ejection time index	396.0	± 2.1 millisec
Tension-time product	27.96	± 0.33
$1/(PEP)^2$	74.3	± 3.0 L/sec^2
Aortic dP/dt	818.0	± 30 torr/sec
IJ wave of the Bcg	2.74	± 0.09 cm
Finger flow	40.2	± 3.6 ml/100g
Forearm flow	3.8	± 0.3 ml/100g
Forearm vascular resistance	28.9	± 1.9 torr/ml/100g
Forearm venous compliance	0.19	± 0.03 ml/100g/torr

allowed the subject to breathe spontaneously for 15 minutes and then repeated our measurements. The end-tidal concentration was once again increased to 1.5 MAC, the volunteer continued to breathe spontaneously for 15 minutes, and we again repeated our measurements. We attempted 2 MAC (3.72%), but found that the subjects became apneic for prolonged periods.

Between the 3rd and 6th hours the effects of transient additions of N_2O and nitrogen to 1 and 1.5 MAC enflurane were studied under conditions of eucapnia.[11] The identical sequences of controlled and spontaneous studies at 1 and 1.5 MAC were repeated in 11 subjects breathing O_2 during the 6th and 7th hours of continuous anesthesia. The arterial pressure line was partially damped in the 12th subject, obliging us to ignore those results in our calculations. Since we saw less respiratory depression during the 7th hour, we tested 8 of the volunteers at 2 MAC.

Student's *t*-tests were employed for statistical comparison. Values were accepted as significant when p was less than 0.05. All cardiovascular variables are presented as percent changes from control except central venous pressure. Base excess, pH, Pao_2, $Paco_2$, tidal volume, minute ventilation and respiratory rate have been reported as the absolute arithmetical differences from the awake volume.

RESULTS

Control ventilatory and cardiovascular values were within normal limits (tables 1 and 2) except for a high skin (finger) blood flow. The high skin flow may have been related to the warmth of the room.

Ventilatory Effects — During the early period of anesthesia, enflurane caused a dose-related depression of ventilation, as evidenced by a significant increase in $Paco_2$ and significant decreases in pH and tidal

TABLE 2

Effects of Concentration and Duration of Enflurane on Ventilation

	N	Alveolar concentration (%)	V_E (L/min)	V_T (ml)	f/min	P_{aCO_2} (torr)	P_{aO_2} (torr)	pH	Base excess	Temperature (C)
Control	12	Awake	9.63 ± .5	730 ± 70	14.2 ± 1.4	35.9 ± 1.1	539 ± 14	7.41 ± .01	−2.2 ± .6	36.4 ± 0.1
Second hour	12	1.86	6.93 ± .4[1]	285 ± 20[1]	24.3 ± .7[1]	61.1 ± 2.4[1]	500 ± 18	7.22 ± .02[1]	−4.3 ± .9[1]	36.3 ± 0.1
	12	2.79	6.08 ± 3.3[2]	200 ± 20[2]	31.5 ± 2.2[2]	76.0 ± 3.3[2]	479 ± 17	7.15 ± .02[2]	−5.5 ± .7	36.2 ± 0.1
Seventh hour	11	1.86	10.3 ± .5[3]	450 ± 40[3]	24.5 ± 3.1	45.9 ± 0.3[3]	507 ± 8	7.29 ± .01[3]	−5.1 ± .7	37.0 ± 0.2[3]
	11	2.79	8.67 ± .5[2,3,4]	300 ± 30[2,3]	31.2 ± 2.7[2,4]	56.1 ± 3.1[2,3]	494 ± 8	7.23 ± .01[2,3]	−5.5 ± .7	36.8 ± 0.3[3,4]
	8	3.72	8.41 ± .6[4]	240 ± 30	37.7 ± 3.0	67.1 ± 4.2[2]	419 ± 29[2]	7.18 ± .02[2]	−5.0 ± 1.4	37.1 ± 0.2[4]

All values are given as the mean ± standard error of the mean (SEM).

Differences are considered significant when $p<0.05$.

[1]Differs significantly between 1.86% end-tidal 2nd hour versus awake

[2]Differs significantly after 0.93% end-tidal increase in same time period

[3]Differs significantly between equipotent values 2nd versus 7th hour

[4]Differs significantly after 0.93% end-tidal increase 7th versus 2nd hour

(a) 2.79% end-tidal 7th hour versus 1.86% 2nd hour

(b) 3.72% end-tidal 7th hour versus 2.79% 2nd hour

volume (table 2, fig 1). Despite a dose-related tachypnea, minute volume decreased significantly. Base excess decreased with the onset of anesthesia, but remained relatively constant during the course of the study.

Five additional hours of anesthesia brought a significant lessening of respiratory depression in the 11 subjects tested (table 2, fig 1). At 1 MAC the $Paco_2$ was 45.9 ± 3.0 mm Hg, which was significantly less than that found at 1 MAC earlier and is similar to that found in a sleeping man.[12] It now required a concentration 0.5 MAC higher to achieve the level of depression seen earlier (eg, 1.5 and 2 MAC now gave the same $Paco_2$ as 1 and 1.5 MAC in the earlier part of the study). At each MAC level tested, the $Paco_2$ was lower, and tidal and minute ventilation significantly greater.

Cardiovascular Effects—Unlike our observations during controlled ventilation, CO was increased roughly in proportion to $Paco_2$, rather than to anesthetic depth (table 3).[10] Although indicating some depression, most indices of myocardial function (Bcg IJ amplitude, aortic dP/dt) did not show the dramatic depression seen with eucapnia, and one index ($1/(PEP)^2$) showed stimulation. Systemic vascular resistance and arterial pressure were reduced in a fashion which failed to correlate with anesthetic dose. Although left ventricular stroke work was reduced by the reduction in pressure, left ventricular minute work and left ventricular SV remained nearer control because of a 40 to 60% increase in HR.

As might have been expected from the high initial values, finger (skin) blood flow did not change significantly (table 4). Forearm (muscle) blood flow increased secondarily to a decrease in forearm vascular resistance. Flow increased and resistance decreased further with the increase from 1 to 1.5 MAC. Forearm venous compliance was

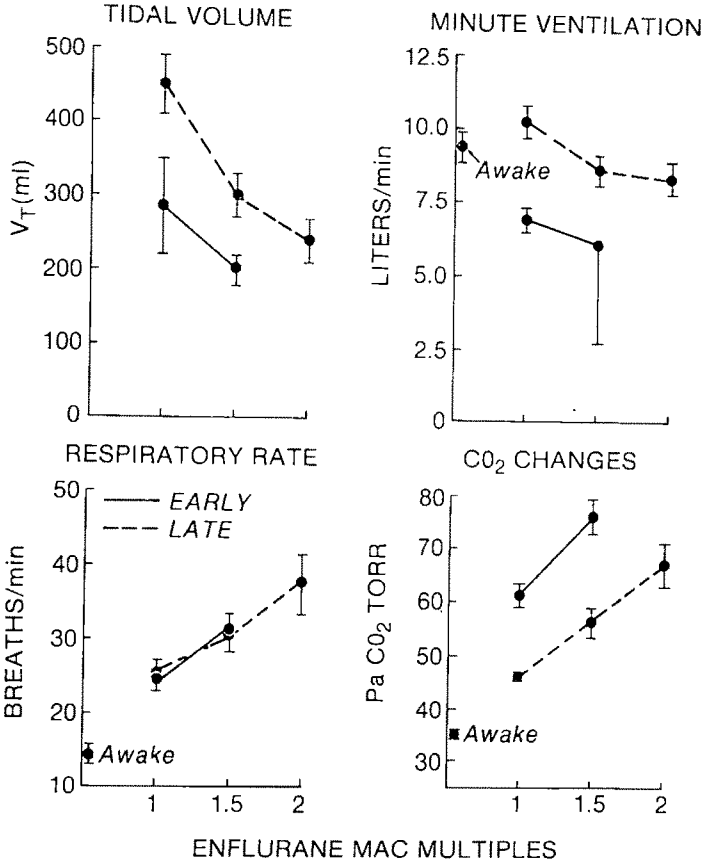


FIG 1. Respiratory effects of continuous enflurane anesthesia during the 2nd hour (———) and the 7th hour (- - - -). Vertical bars represent ± standard error of the mean. Tidal volume awake 730 ± 70 ml is not depicted in the figure.

TABLE 3
Cardiovascular Effects of Enflurane During Spontaneous Ventilation

	Number of subjects	Alveolar concentration	Cardiac output	Mean arterial pressure	Systemic vascular resistance	Heart rate	Stroke volume	Central venous pressure	Bcg IJ amplitude	Aortic dP/dt
Second hour	12	1.86	+31.2 ± 8.0[1]	−37.7 ± 5.5[1]	−51.6 ± 5.3[1]	+40.9 ± 4.6[1]	− 7.2 ± 4.2	+0.1 ± 0.8	− 6.0 ± 6.3	−37.7 ± 5.9[1]
	12	2.79	+54.5 ± 9.2[2]	−35.0 ± 2.7	−58.4 ± 3.8	+62.7 ± 5.2[2]	− 5.0 ± 4.6	+1.2 ± 0.9	+10.3 ± 7.3[2]	−21.3 ± 7.1[2]
Seventh hour	11	1.86	+38.1 ± 12.0	−24.6 ± 2.9	−44.9 ± 3.9	+54.8 ± 7.7[3]	−12.0 ± 4.1	+1.6 ± 0.9	− 5.2 ± 8.2	−36.4 ± 5.9
	11	2.79	+44.3 ± 12.8	−33.9 ± 2.9[2]	−54.0 ± 4.3	+62.0 ± 6.7	−11.7 ± 5.2	+1.3 ± 1.0	−18.3 ± 7.4[2,3]	−46.8 ± 5.9[2,3]
	8	3.79	+44.3 ± 14.1	−41.0 ± 3.8[2]	−62.6 ± 3.4[2]	+61.6 ± 6.5	−11.1 ± 6.3	+0.7 ± 1.0	−11.0 ± 10.1	−45.0 ± 6.0

	Number of subjects	Alveolar concentration	1/(PEP)[2]	Mean rate of LV ejection	LV work	LV stroke work	LV stroke power	Ejection time index	Tension-time product
Second hour	12	1.86	+ 23.0 ± 13.3	−5.1 ± 3.7	−20.5 ± 7.9[1]	−43.2 ± 5.1[1]	−41.9 ± 5.3[1]	+ 8.4 ± 1.3[1]	−39.3 ± 5.1[1]
	12	2.79	+ 92.8 ± 29.4[2]	+0.9 ± 4.5	− 0.3 ± 6.4	−38.5 ± 3.5	−34.6 ± 3.7	+10.9 ± 1.2	−39.0 ± 2.6
Seventh hour	11	1.86	+ 38.1 ± 11.7	−6.8 ± 5.1	+ 5.0 ± 10.6	−33.5 ± 4.0	−29.3 ± 5.2	+ 9.6 ± 1.2	−28.6 ± 2.2[3]
	11	2.79	+ 69.0 ± 32.9	−7.0 ± 5.3	− 5.1 ± 8.4	−41.8 ± 3.8	−38.2 ± 5.0	+11.4 ± 2.2	−37.5 ± 1.7[2]
	8	3.72	+134.0 ± 37.8	−6.1 ± 8.8	−13.8 ± 13.4	−47.7 ± 6.5	−43.9 ± 8.4	+12.3 ± 1.7	−45.0 ± 2.5[2]

All values are percent change from control except central venous pressure, which is torr change from control.

All values are the mean ± standard error of the mean (SEM).

All symbols of significant difference demonstrate a $p<0.05$.

[1] 1 MAC, 2nd hour significantly different from awake control

[2] Significant difference after 0.5 MAC increase in the same time period

[3] Significant difference between equipotent levels, 2nd versus 7th hour

TABLE 4
Percent Changes in Finger (Skin) and Forearm (Muscle) Blood Flow During Enflurane Anesthesia With Spontaneous Ventilation

	Finger flow	Forearm flow	Forearm vascular resistance	Forearm venous compliance
Second hour				
1 MAC	+93.7 ± 45.7	+149.6 ± 32.5[1]	−70.5 ± 3.3[1]	−52.0 ± 16.5
1.5 MAC	+64.3 ± 25.9	+203.6 ± 32.3	−78.0 ± 2.3	−20.1 ± 17.8
Seventh hour				
1 MAC	+ 0.3 ± 76.0	+110.3 ± 43.9	−50.7 ± 3.2[3]	−15.5 ± 17.2
1.5 MAC	− 6.5 ± 42.9	+133.3 ± 42.9	−68.3 ± 4.3[2]	−27.0 ± 20.1
2.0 MAC	+68.0 ± 99.4	+141.5 ± 50.0	−73.2 ± 5.0	−13.0 ± 39.4

All symbols of significant differences demonstrate a $p<0.05$.

[1]1 MAC, 2nd hour significantly different from awake control
[2]Significant difference after 0.5 MAC increase in the same time period
[3]Significant difference between equipotent levels, 2nd versus 7th hour

reduced at all levels of anesthesia, perhaps because the veins were distended to begin with and therefore were on a flatter portion of the compliance curve.

There were few significant time-related cardiovascular effects. Bcg IJ wave amplitude and aortic dP/dt both showed significantly greater depression at 1.5 MAC during the 7th hour (table 3).

DISCUSSION

The profound cardiovascular depression seen during enflurane anesthesia when ventilation is controlled and $Paco_2$ is normal does not occur or is attentuated when ventilation is spontaneous.[10] Striking significant differences between the two modes of ventilation are seen with several variables. At 1 MAC with spontaneous ventilation, CO was 57% higher than during controlled ventilation at equipotent enflurane concentrations. Similarly, the difference in SV was 32%, muscle blood flow 152%, and HR 18%. Comparison between values at 1.5 MAC produced even greater differences in some variables. This disparity suggests a beta-sympathetic-like stimulation, a consequence of a reflex response to an elevated arterial CO_2 concentrations.[13] Compared with the awake values, indices of cardiovascular function were increased or were less decreased during spontaneous breathing. These included the Bcg IJ wave, aortic dP/dt, $1/(PEP)^2$, mean rate of left ventricular ejection, ejection time index, left ventricular work, left ventricular stroke work, and left ventricular stroke power. One variable not altered by the spontaneous ventilatory patterns was mean arterial pressure, which remained nearly constant due to a 52% decrease in systemic vascular resistance. The decrease in systemic vascular resistance caused by enflurane during spontaneous ventilation is the greatest seen with any anesthetic agent tested by this technic.[3,6,14-16] The decrease is comparable to that induced by infusion of nitroprusside in healthy subjects.[17,18]

Our results also confirm that enflurane produces profound respiratory depression during the first few hours of anesthesia. One to 1.5 MAC produces marked elevations in $Paco_2$ and decreases in tidal volume and minute ventilation. The respiratory depression produced by enflurane exceeds that produced by equal levels of isoflurane and slightly greater concentrations of halothane which have been examined in a similar fashion.[3,4]

Prolonged anesthetic exposure significantly reduced the respiratory depression due to enflurane to a greater degree than has been observed with halothane or isoflurane (fig 2).[3,4,19] The degree of recovery approximately equaled a reduction in anesthetic concentration of 0.5 MAC, or 0.93% end-tidal enflurane. After 7 hours of anesthesia, the depression of respiration resulting from enflurane no longer differed significantly from that produced by halothane or isoflurane. At this time, the resting $Paco_2$ associated with a given MAC level was nearly

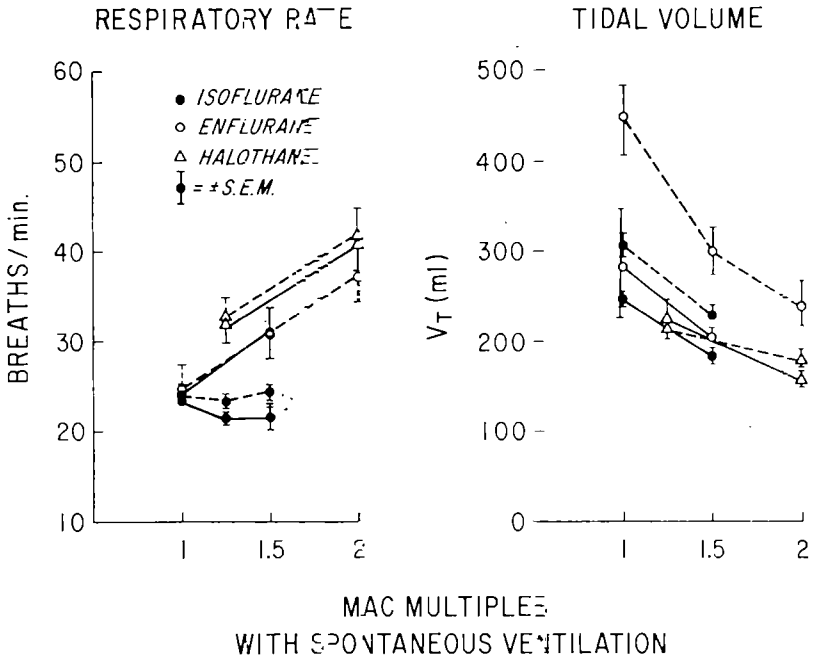


FIG 2. Respiratory responses during the 1st hour of halothane and isoflurane and during the 2nd hour of enflurane (———) and again during the 5th hour of halothane and isoflurane and during the 7th hour of enflurane (- - - -). Vertical bars indicate standard error of the mean.

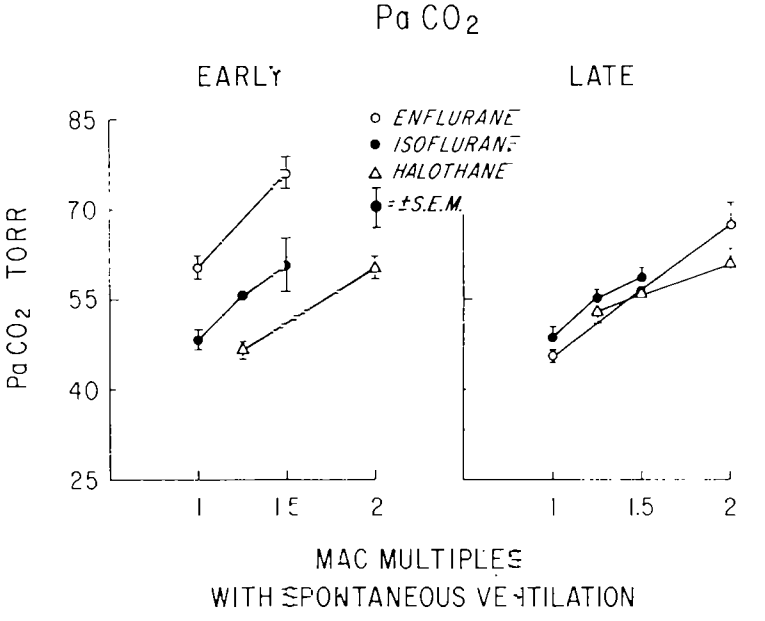


FIG 3. $Paco_2$ changes produced during the 1st hour of halothane and isoflurane and during the 2nd hour of enflurane and again during the 5th hour of halothane and isoflurane. Vertical bars indicate standard error of the mean.

identical for all agents (fig 3). The convergence of the level of depression for the three agents resulted principally from an increased tidal volume associated with enflurane.

During mechanical ventilation, some of the cardiovascular depression tended to be reversed with the passage of time. This was not observed with spontaneous ventilation. As a consequence, the differences between

the cardiovascular effects obtained with spontaneous versus controlled ventilation were narrowed. Price and his associates[20] have suggested that the cardiovascular stimulation seen with prolonged halothane anesthesia is due to beta-adrenergic stimulation. The studies with controlled ventilation did indicate that a temporally related beta-sympathetic-like effect is present with enflurane. The apparent absence of this cardiovascular stimulation with enflurane during spontaneous ventilation may have resulted from two counterbalancing effects. The reduction in $Paco_2$ between the 2nd and 7th hours would oppose and disguise the time-related stimulation by decreasing the central stimulation produced by CO_2.

We have demonstrated that enflurane is a potent respiratory depressant in unstimulated man. Despite this depression, the cardiovascular system remains responsive to the beta-sympathetic stimulation initiated by hypercapnia. The price paid for this is an initial marked hypercapnia in an unstimulated patient in the first hours after induction. In the clinical setting, however, hypercapnia may be diminished by the stimulus of surgery or adversely augmented by premedication. After 7 hours—or less—of anesthesia, respiratory depression and hypercapnia are significantly decreased.

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Cardiovascular Effects of Enflurane Anesthesia During Controlled Ventilation in Man

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We studied the cardiovascular effects of enflurane in 12 unpremedicated volunteers without surgery under conditions of constant arterial CO_2 tension and body temperature. During the first hour of anesthesia 1 MAC (1.86% end-tidal) was associated with decreased cardiac output (CO) by 25.9%, stroke volume (SV) by 39.6%, systemic vascular resistance (SVR) by 16.1%, IJ wave of the ballistocardiogram (Bcg) by 39%, and aortic dP/dt by 60.7% compared to awake values. Heart rate (HR) increased 22.4%, but blood pressure (BP) declined by 36%. Central venous pressure (CVP) rose less than 1 torr. Plethysmographic measurements of finger (skin) and forearm (muscle) blood flow did not significantly change from awake levels, but forearm vascular resistance was reduced. An increase to 1.5 MAC caused further declines in SV, aortic dP/dt, and Bcg, but not in BP or CO. Heart rate increased and the CVP rose 3.8 torr above control. Two MAC enflurane could not be achieved without progressive and profound hypotension.

During the sixth hour of continuous anesthesia, we observed some recovery of cardiovascular performance. Cardiac output, SV, and aortic dP/dt returned toward awake levels at 1 MAC, but not at 1.5 MAC. Systemic vascular resistance declined during the interval, and BP remained unaltered.

The margin of safety between concentrations of enflurane required for surgical anesthesia and hazardous concentrations is less during controlled ventilation than is the margin of safety associated with other potent inhalation anesthetics.

Key Words—ANESTHETICS, volatile, enflurane. HEART, cardiac output, myocardial function. BLOOD PRESSURE, systemic vascular resistance.

SEVERAL studies were reported concerning the cardiovascular effects of enflurane prior to its introduction in 1972 as an anesthetic approved for clinical practice.[1-6] Other reports have followed since then.[7-9] However, none of these investigations has included comprehensive awake control data for a study performed in healthy subjects of uniform age in the absence of modifying factors such as premedication, surgical stress, other anesthetic or adjuvant drugs and variations in arterial CO_2 tension, end-tidal an-

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esthetic concentration, or body temperature. The influence of the duration of anesthesia has not been well documented. We shall report investigations in which these factors were controlled and the effect of continued anesthesia examined.

METHODS

We studied 12 healthy, unpremedicated male volunteer subjects 22.5 ± 0.5 (SEM) years of age. The Human Research Committees of the University of California, San Diego, and the Veterans Administration Hospital, San Diego, approved the study. Each volunteer gave informed consent. Complete medical histories were obtained and thorough physical examinations performed. Each subject had a normal 12-lead ECG, chest roentgenogram, and laboratory studies which included bromsulfophthalein excretion, a complete blood count and urinalysis, and serum levels of electrolytes, creatinine, blood urea nitrogen, uric acid, albumin, globulin, SGOT, SGPT, LDH, CPK, and alkaline phosphatase. We obtained two electroencephalograms in each subject prior to the study. Several potential volunteers were disqualified at each stage of the selection process.

Studies were performed in a large room adjacent to an intensive care unit. Resuscitation equipment was available in the study room. The room was warmed during anesthesia to aid in maintenance of normothermia. The volunteers reported after fasting for at least 8 hours. After infiltrating lidocaine 1.5% subcutaneously, we cannulated the left axillary artery (10 subjects) or brachial artery (2 subjects), a right forearm vein, and the left antecubital vein. The arterial cannulae were connected to Teflon catheters 20 cm in length. We applied central manubrium-V_5 ECG leads and monitored an 8-channel electroencephalogram. A recording microphone was positioned over the base of the heart for phonocardiograph recording. Skin and oral (awake) and esophageal (anesthetized) temperatures were measured with thermistors. During the study the subjects received an average of 1558 ± 50 (SEM) ml of 0.45% saline in 5% dextrose solution.

Arterial, central venous, and peripheral venous pressures were measured directly via Statham transducers with the means obtained by electronic damping. Cardiac output was determined by the dye-dilution technic. We calculated cardiac-cycle intervals from the ECG, arterial pressure wave, and phonocardiograph recordings.[10] The first derivative of arterial pressure (dP/dt) was obtained via a calibrated Hewlett-Packard Derivative Computer. Filtering of the output was accomplished at 50 Hz (−3 db) at a rolloff of 12 db per octave. Mean arterial pressure was multiplied by ejection time to provide the tension-time product. Total systemic vascular resistance (SVR) was calculated by dividing cardiac output (CO) into the difference between mean arterial and mean central venous pressures. We determined O_2 consumption by multiplying CO by the difference between arterial and central venous O_2 contents. Because we took central venous, rather than pulmonary artery samples, venous O_2 content may be inaccurate. However, since our intent was to measure changes in O_2 consumption rather than absolute values, this omission may be unimportant. Details of these measurements are provided in our previous communications.[11-13]

The subjects rested on an ultra-low-frequency air-bearing ballistocardiograph bed weighing 3 kg, undamped, with a natural frequency of 0.18 Hz. All tubing, including that connected to the endotracheal tube, was suspended vertically from a pole to minimize damping. The tubing connected to the endotracheal tube was very flexible and light. Acceleration was transduced in the head-foot (y) axis with a piezoresistive accelerometer. An air mattress under the subject was inflated periodically and the subject passively exercised to relieve pressure over bony prominences.

Whitney strain gauges were placed around the forearm and third finger for estimation of muscle (forearm) and skin (finger) blood flow by occlusion plethysmography.[11] Occlusion cuffs were placed on the base of the third finger and lower arm. When measuring forearm blood flow, perfusion of the hand was occluded at the wrist. Forearm vascular resistance was calculated by dividing the difference between mean arterial pressure and central venous pressure (CVP) by forearm blood flow. Forearm venous compliance was obtained by calculating the ratio of change in forearm blood volume/minute to change in forearm venous pressure/minute.

Control measurements were taken with the subject awake in the supine position while breathing room air and repeated with the subject breathing pure O_2 via a mouth-

piece. The nose was occluded by a clip. After a subject became accustomed to the apparatus, ventilation was changed from spontaneous to controlled through an Ohio Series 300/DO Ventilator. Ventilator controls were adjusted until the subject could accept passive ventilation comfortably. After 15 minutes of controlled ventilation, all measurements were repeated until consistent CO readings were obtained, which were used to compare with anesthetized values.

After a brief rest period, we induced anesthesia with enflurane and O_2 via face mask and subsequently inserted a cuffed endotracheal tube. Succinylcholine 40 mg was administered to 3 subjects to facilitate intubation. Continuous (end-tidal) enflurane and CO_2 concentrations were measured via catheters placed in the endotracheal tube and connected to Beckman LB-2 analyzers whose outputs were displayed on the multichannel recorders employed for cardiovascular measurements. These data were also preserved on magnetic tape.

The concentration of enflurane was adjusted to 1 MAC, which is 1.86% in this age group.* After 1 MAC had been maintained for 10 minutes with ventilation controlled to provide normocapnia, all measurements were repeated. The concentration was increased to 1.5 MAC (2.79% end-tidal), maintained for 10 minutes, and all measurements again repeated. Ten minutes of equilibration was selected after several trials of 20 minutes of equilibration revealed no further significant changes in the longer time period. We transiently imposed 2 MAC during 5 studies, but profound depression of blood pressure, twice initiated by isorhythmic dissociation of atrial and ventricular contraction, obliged us to discontinue 2 MAC on 4 occasions. Since it was apparent that we would not be able to achieve 2 MAC safely, we did not attempt studies at this level in the remaining 7 subjects. The measurements at 1 and 1.5 MAC constituted our data for the 1st hour of anesthesia. During the 6th hour of anesthesia, measurements were repeated with the same 1 and 1.5 MAC sequence. Again, we could not achieve 2 MAC without risking undue depression. Between the 2nd and 6th hours, the cardiovascular effects of enflurane anesthesia during spontaneous ventilation at 1 and 1.5 MAC[16] and the effect of the addition of N_2O to 1 and 1.5 MAC enflurane were studied.[17]

*The minimum alveolar concentration (MAC) required to eliminate movement in response to a surgical incision in 50% of patients varies inversely with age.[14] Gion and Saidman's[15] MAC for enflurane was 1.68% for patients whose mean age was 39 years. We estimate a value of 1.86% in 20-to-30-year-old adults.

Statistical comparisons were made using paired Student's *t*-tests. Values were accepted as significant when p was less than 0.05. The data have been presented as the mean ± standard error of the mean (SEM). All values during anesthesia have been expressed as percentage changes from control except CVP, base excess, O_2 consumption, esophageal temperature, pH, Pao_2, and $Paco_2$, which have been reported as the absolute arithmetical differences from the awake values.

RESULTS

Table 1 lists control values from all subjects. Since neither the type of ventilation nor inspired O_2 concentrations had any significant effect, all data are pooled. Tables 2 and 3 and fig 1, 2, and 3 demonstrate the results of our measurements during anesthesia. Normothermia was maintained throughout anesthesia and $Paco_2$ held constant at awake levels.

First Hour—During the 1st hour of anesthesia we found that enflurane exerted a pronounced cardiac depressant effect at 1 MAC and a still greater effect at 1.5 MAC. At 1 MAC, mean arterial pressure decreased significantly due to a moderate decrease in SVR and a greater decrement in CO (fig 1). A significant increase in HR only partly compensated for the decreased stroke volume (SV). Central venous pressure rose less than 1 torr. Indices of myocardial function, namely aortic dP/dt, the IJ wave of the ballistocardiogram, $1/(PEP)^2$, and mean rate of left ventricular ejection paralleled the decrease in CO (fig 2). Significant decreases in derived values for left ventricular minute and stroke work, left ventricular stroke power, and the tension-time product were seen (fig 3). Skin temperature increased following induction of anesthesia. Forearm (muscle) and finger (skin) blood flows remained near awake values despite the reduction in cardiac output (table 2). Forearm vascular resistance decreased 38%, while forearm venous compliance rose 47%. Oxygen consumption decreased more than did CO (table 3). Base excess decreased with the onset of anesthesia but did not vary significantly thereafter.

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TABLE 1
Data in the Awake (Control) Period (Mean ± SEM)

Age	22.5	± 0.5 years
Height	179.3	± 1.3 cm
Weight	74.7	± 2.8 kg
Cardiac output	5.36	± 0.12 L/min
Heart rate	62.0	± 1 beats/min
Stroke volume	86.6	± 1.5 ml
Mean right atrial pressure	5.0	± 0.4 torr
Mean arterial pressure	94.0	± 1.0 torr
Systemic vascular resistance	1365.0	± 39.0 ohms
Left ventricular minute work	6.78	± 0.5 joules
Left ventricular stroke work	0.1095	± 0.0 joules
Left ventricular stroke power	0.369	± 0.01 watts
Mean rate of left ventricular ejection	0.292	± 0.01 ml/sec
Ejection time index	396.0	± 2.1 millisec
Tension-time product	27.96	± 0.33
$1/(PEP)^2$	74.3	± 3.0 $1/sec^2$
Aortic dP/dt	818.0	± 30 torr/sec
IJ wave of the Bcg	2.74	± 0.09 cm
Finger flow	40.2	± 3.6 ml/100g
Forearm flow	3.8	± 0.3 ml/100g
Forearm vascular resistance	28.9	± 1.9 torr/ml/100g
Forearm venous compliance	0.19	± 0.03 ml/100g/torr

TABLE 2
Percent Changes in Finger and Forearm Blood Flow During Enflurane Anesthesia

	Number of subjects	Finger flow	Forearm flow	Forearm vascular resistance	Forearm venous compliance
First hour					
1 MAC	12	+40 ± 22	− 2 ± 6	−38 ± 4*	+47 ± 35
1.5 MAC	12	+31 ± 35	− 9 ± 9	−41 ± 5	+25 ± 30
Sixth hour					
1 MAC	11	−22 ± 24	+66 ± 29†	−51 ± 8	+0.5 ± 24
1.5 MAC	11	+ 9 ± 32	+73 ± 39	−61 ± 6	+ 1 ± 21

All values are percent change from control.
All values are the mean ± standard error of the mean (SEM).
All symbols of significant differences demonstrate $p<0.05$.
*Significant difference from awake value
†Significant difference between equipotent levels, 1st versus 6th hour

Increasing enflurane to 1.5 MAC did not further alter significantly mean arterial pressure, SVR, or CO. Heart rate accelerated, but SV decreased in association with further declines in aortic dP/dt, the IJ wave of the ballistocardiogram, left ventricular stroke work and power, the ejection time and tension-time product, and the mean rate of left ventricular ejection. Central venous pressure increased less than 4 torr above control.

The subjects' ECG's were free of ven-

TABLE 3
Temperature, Blood Gas Values, and Oxygen Consumption

	Number of subjects	Temperature (C)	P_{ACO_2} (torr)	P_{ACO_2} (torr)	pH	Base excess (mEq)	Oxygen consumption (ml/min)
Control	12	36.4 ± 0.1	546 ± 33	36.8 ± 0.6	7.39 ± 0.01	−2.3 ± 0.7	245 ± 20
First hour							
1 MAC	12	36.3 ± 0.1	508 ± 20	37.9 ± 0.5	7.35 ± 0.01*	−4.9 ± 0.9*	155 ± 19*
1.5 MAC	12	36.4 ± 0.1	499 ± 17	36.4 ± 0.6	7.35 ± 0.01	−5.0 ± 0.8	166 ± 25
Sixth hour							
1 MAC	11	36.8 ± 0.2†	522 ± 13	37.0 ± 0.3	7.35 ± 0.01	−4.8 ± 0.7	206 ± 15†
1.5 MAC	11	36.8 ± 0.2	504 ± 12	37.2 ± 0.4	7.35 ± 0.02	−4.8 ± 0.8	174 ± 12

All values are the mean ± standard error of the mean (SEM).
*Significantly different ($p<0.05$) from the awake value.
†Significant difference between equipotent levels, 1st versus 6th hour.

tricular cysrhythmias. Five volunteers developed episodes of isorhythmic dissociation of atrial and ventricular contraction (IRD) in which the PR interval progressively shortened until the P wave disappeared within the QRS complex.* This was associated with an abrupt decrease in mean arterial pressure of 10 to 20 torr, a decrease which persisted until sinus rhythm returned 3 to 57 minutes later.

Sixth Hour—We observed some reversal of cardiovascular depression after 6 hours of continuous anesthesia (fig 1, 2, and 3). At 1 MAC, CO returned to awake values as a result of some recovery of the depression of SV and continued tachycardia. The increase in SV was associated with significant increases in aortic dP/dt, the mean rate of the left ventricular ejection, stroke work and power, but not in the acceleration ballistocardiogram. The recovery of CO was not accompanied by an elevation of blood pressure (BP). Mean arterial pressure remained unchanged, as the increase in CO was concurrent with a fall in SVR. Muscle (forearm) blood flow increased modestly, while skin (finger) flow declined. Central venous pressure did not change significantly over time.

Equilibration at 1.5 MAC decreased BP and CO, despite continued tachycardia. Two MAC still caused profound hypotension. There was no evidence of significant accommodation of arterial pressure at deeper levels with continued anesthesia.

DISCUSSION

Enflurane produces a dose-related cardiovascular depression in the unstimulated young, healthy subject. Cardiovascular instability results from anesthetic concentrations exceeding 1.5 MAC. During the 1st hour of anesthesia, the major effect is a dose-related depression of SV with a lesser decrease in SVR. Tachycardia was observed consistently, but this response only partially compensated for decreased SV. We observed that the marked acute depression of cardiac function following increases in concentration did not diminish as the end-tidal concentration was held constant.

During prolonged enflurane anesthesia, myocardial function recovered partially at

*Smith NT, Calverley RK, Jones CW, et al: The hemodynamic impact of atrial arrhythmias during enflurane anesthesia in man. Scientific Abstracts of the 1977 Meeting of the American Society of Anesthesiologists, pp 99-100

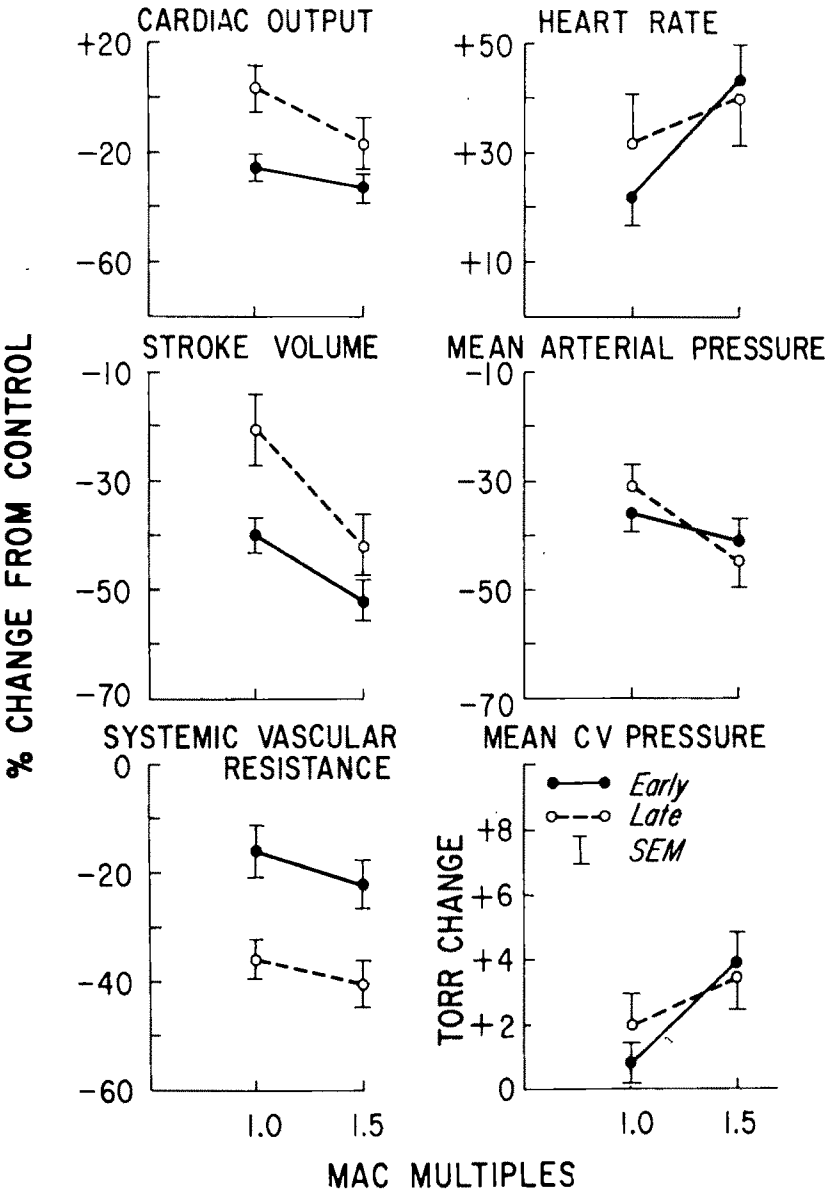


FIG 1. Percent changes in some cardiovascular values during continuous enflurane anesthesia from control levels in the 1st hour (———) and in the 6th hour (- - - -) of anesthesia. Vertical bars represent ± standard error of the mean.

light, but not deeper, levels of anesthesia. Although CO increased, the early depression of arterial pressure persisted due to a concurrent decrease in SVR. The phenomenon of recovery of cardiac function has been described previously with other inhalation agents. Cardiac output increased between the 1st and 5th hour of anesthesia with halothane,[13] fluroxene,[12] cyclopropane,[11] and diethyl ether.[18]

Price et al[19] considered and discarded several factors as potential causes for the time-related circulatory stimulation during halothane anesthesia, including expanded plasma volume, increased whole-body O_2 requirement, metabolic acidosis, and discomfort and immobility. Pretreatment with beta-receptor blocking agents eliminated the time-related cardiovascular changes during halothane anesthesia, suggesting that these changes were mediated by *beta*-adrenergic stimulation. While enflurane has not been shown to cause sustained sympathetic ex-

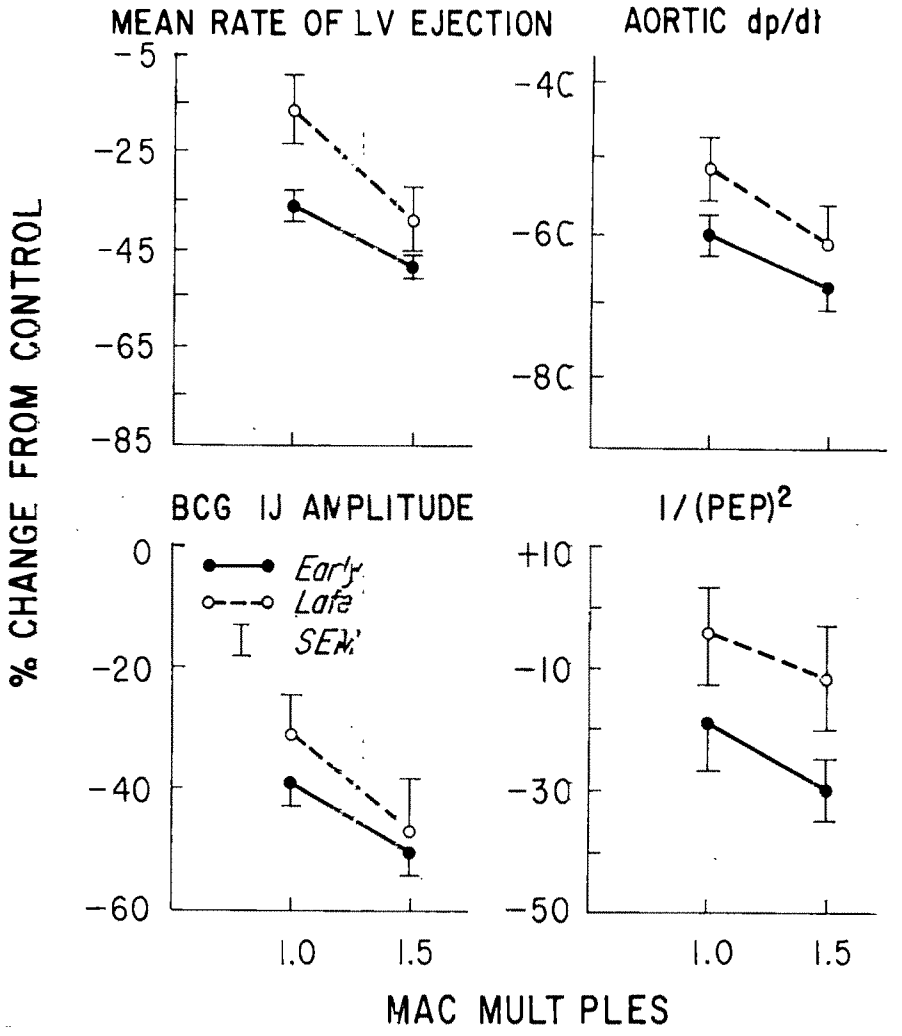


FIG 2. Additional percent changes in cardiovascular function during continuous enflurane anesthesia from control levels in the 1st hour (_____) and in the 6th hour (- - - -) of anesthesia. Vertical bars represent ± standard error of the mean.

citation, it is possible that a similar response caused the increase in SV and decrease in SVR resistance seen in our study late in the course of continuous enflurane anesthesia.

Perhaps the use of spontaneous ventilation,[16] as well as occasional bursts of N_2O, during the 5-hour interval may have caused the time-related sympathetic stimulation seen with enflurane. However, Price et al[19] and Cullen et al[12] have observed this phenomenon with halothane and fluroxene, respectively, with such interventions.

In contrast, prolonged anesthesia with isoflurane, an isomer of enflurane, has not been associated with temporally related cardiovascular stimulation.[20] Neither does isoflurane depress CO in clinical concentrations. These disparities are two of the intriguing differences between enflurane and isoflurane.

Of all the agents which we have studied,[11-13, 8,20] enflurane possesses the narrowest margin of safety between concentrations required for surgical anesthesia and hazardous levels. Other inhalation anesthetics may be administered to the unstimulated subject in concentrations in excess of 1.5 MAC without the cardiovascular decompensation and hypotension observed in this study.

We recognize that the data obtained from

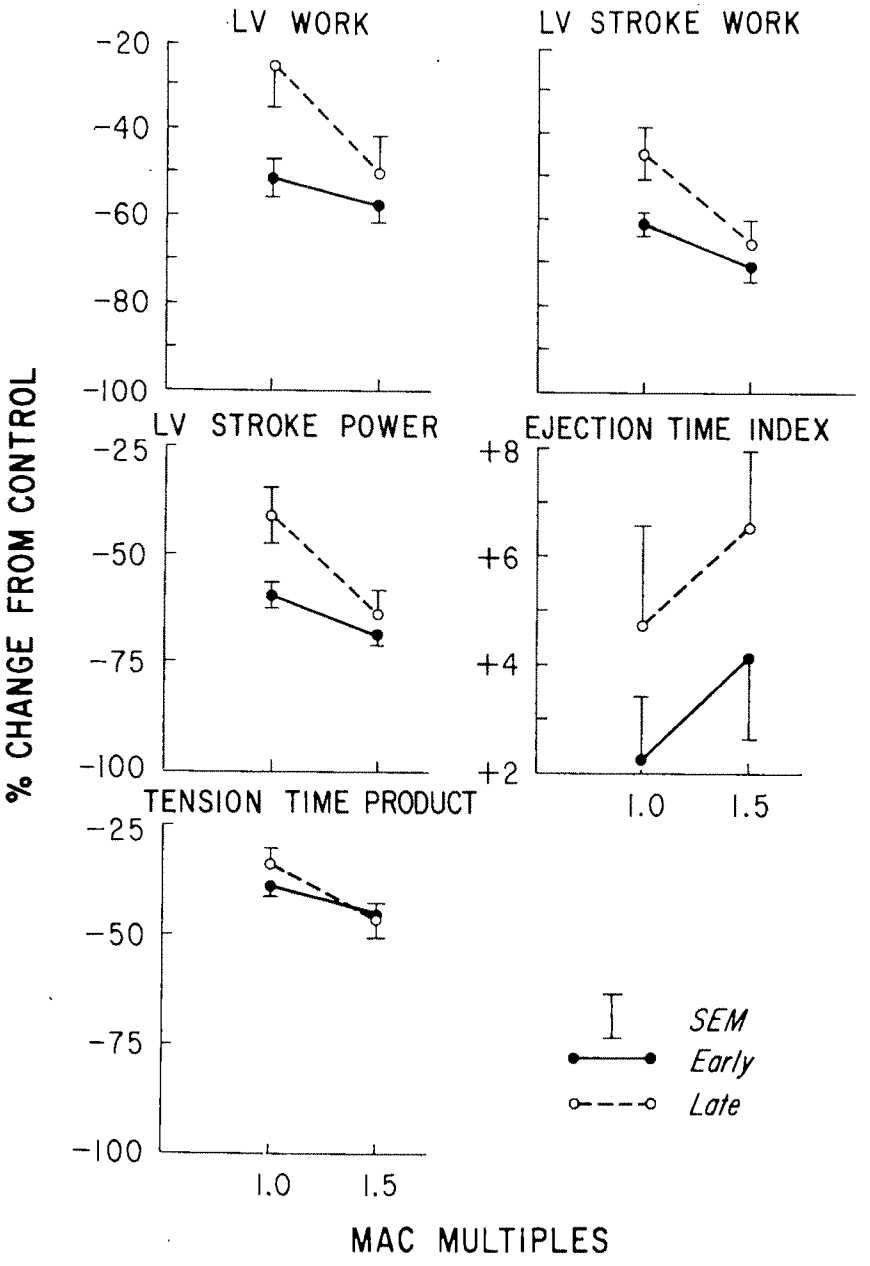


FIG 3. Percent changes in derived cardiovascular function during continuous enflurane anesthesia from control values in the 1st hour (_____) and in the 6th hour (- - - -) of anesthesia. Vertical bars represent ± standard error of the mean.

our observations may differ profoundly from those obtained during clinical anesthesia. The experimental protocol obliged us to maintain the subjects in the supine position and restricted fluid replacement to maintenance requirements. The depressant influences of enflurane would be considerably modified, and perhaps negated, by the stimulus of surgery, by fluid replacement to augment the cardiac preload, by modifications of posture to improve venous return, by the simultaneous administration of N_2O to reduce enflurane requirements,[17] or by hypercapnia, which stimulates the sympathetic nervous system.[16] This last factor, hypercapnia, is perhaps one of the most important ones, and is discussed in detail in the companion paper.[16] Essentially, hypercapnia with spontaneous ventilation with enflurane produces a *beta*-adrenergic like picture, with

increased HR and CO and decreased contractility.

On the other hand, several factors could cause even greater depression in the clinical setting. These include advanced age,[21] decreased cardiac reserves, and hypovolemia secondary to a pre-existing fluid deficit or acute blood loss. Mild hypothermia is not uncommon in air-conditioned operating rooms and could decrease cardiac performance. Patients also usually receive premedicants and other drugs. For example, propranolol, which would limit cardiac acceleration in response to decreased SV, is poorly tolerated during experimental enflurane anesthesia.[22]

Systemic hypotension is a consistent sign of excessive enflurane concentrations. This may be a fortunate warning, as systemic BP is routinely monitored by all anesthetists. Clinicians are accustomed to responding to hypotension by decreasing anesthetic concentration. This action prevents the progression toward hazardous levels of enflurane anesthesia.

We found no deleterious sequelae to the cardiovascular depression seen with enflurane anesthesia. During these studies, the EEG was monitored and recorded continuously.* We did not identify any signs of cerebral ischemia. The ECG did not display any signs of myocardial hypoxia. No ST segment depression or ventricular dysrhythmias were recorded. At the same time, there was no evidence of metabolic acidosis, as the base deficit did not increase. This suggests that total body metabolic demands were met at all times. Central venous pressure changes were not of a degree (−3 torr) which would create concern as evidence of cardiovascular decompensation. Finally, our volunteers recovered uneventfully from anesthesia. This assumption is supported by the absence of major biochemical[23] and psychological** derangements, the preservation of satisfactory renal function,[24] the absence of de novo changes in the postanesthetic EEG's[25] and the absence of suppression of lymphocyte transformation[26] in these volunteers.

*Stockard JJ, Burchiel KJ, Smith NT, et al: The effects of nitrous oxide and carbon dioxide on epileptiform EEG activity produced by enflurane. Scientific Abstracts of the 1975 Meeting of the American Society of Anesthesiologists, pp 309-310

**Stark AH, Storms LH, Calverley RK, et al: The effects of enflurane on psychological functioning. Scientific Abstracts of the 1975 Meeting of the American Society of Anesthesiologists, pp 229-230

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POSTOPERATIVE RESPIRATORY CARE

After abdominal surgery 64 patients were managed with either of the following technics of respiratory care: (1) deep breathing encouraged by use of an "incentive spirometer"; or (2) episodic intermittent positive-pressure breathing (IPPB). Both series of patients also received therapy with a nebulized bronchodilator drug. All patients had preoperative spirometric measurements followed by 5 consecutive days of therapy and spirometry. Chest x-ray films were obtained for all patients. There were no significant differences between the 2 methods of respiratory care, but 57% (17/30) of the IPPB group developed pneumonia, atelectasis, or bronchitis, while only 29% (10/34) did so in the group using the "incentive spirometer" ($p<0.05$). There were no significant spirometric differences between groups. Principal conclusions were that (1) deep breathing under the conditions of this investigation was equal to episodic therapy with IPPB; and (2) from an economic standpoint, IPPB, as it is currently practiced, may be disadvantageous when compared with the use of an "incentive spirometer." *(Dohi S, Gold MI: Comparison of two methods of postoperative respiratory care. Chest 73:592-595, 1978)*

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Halothane and Enflurane Protect Against Bronchospasm in an Asthma Dog Model

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Experimental asthma was induced in 6 dogs previously sensitized to ascaris antigen by ventilating them with aerosolyzed ascaris antigen for 10 minutes. Pulmonary resistance was calculated from simultaneous pressure and flow measurements at a lung volume 200 ml above functional residual capacity. Prior to administration of aerosolyzed ascaris antigen, pulmonary resistance was 2.35 ± 0.56 (mean ± SEM) cm H_2O/L/sec in dogs anesthetized with thiopental. Twenty minutes after the end of ascaris antigen administration, pulmonary resistance was 5.72 ± 1.29 in dogs given additional thiopental, 3.18 ± 0.62 in dogs anesthetized with halothane (0.87% inspired concentration), and 3.03 ± 0.30 in dogs anesthetized with enflurane (2.2% inspired concentration). These differences in responses of pulmonary resistance were statistically significant at 0.05 level.

Halothane and enflurane were equally effective in decreasing pulmonary resistance in an ascaris antigen dog model of asthma.

Key Words—LUNG, asthma. ANESTHETICS, volatile, halothane. ANESTHETICS, volatile, enflurane. ANESTHETICS, intravenous, thiopental.

ASTHMATIC patients requiring anesthesia are at higher risk than nonasthmatics. The major problems in asthmatic patients are bronchospasm and cardiac arrhythmias.[1-3] Halothane is a known bronchodilator[2-4] and is now considered the drug of choice in these patients. However, halothane is not an ideal drug because it sensitizes the myocardium to catecholamines.[5] Asthmatic patients often come to surgery pretreated with sympathetic drugs, which may interact with halothane to cause cardiac arrhythmias. Because enflurane does not sensitize the myocardium to catecholamines,[6] it would be a useful anesthetic in asthmatic patients. Its effects on airways are not known and the use of enflurane in asthmatic patients is at this time controversial.[7] We undertook the present study to investigate the effects of enflurane as compared to halothane on airways and resolve the controversy.

METHODS

Ascaris suum worms were obtained from a slaughterhouse and purified according to the method of Mackler et al.[8] The purified preparation contained 3.46 mg protein/ml. Six dogs were studied. Group 1 consisted of three 20-kg mongrel dogs with chronic tracheostomies, selected only because they had positive skin tests to ascaris antigen. Group 2 consisted of three 20-kg dogs, specifically selected because in addition to having positive skin tests to ascaris antigen, their airways were highly reactive to the antigen during thiopental anesthesia.

Unpremedicated dogs were anesthetized standing, supported by a sling, with thiopental 12 mg/kg and paralyzed with succinylcholine. Tracheostomy tubes (Portex) were inserted and the dogs ventilated at a tidal volume of 400 ml and a frequency of 12/min

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using an animal respirator (Harvard Apparatus Company, Millis, Massachusetts) with a 2:1 mixture of N_2O and O_2. Esophageal balloons (Dynasciences, Blue Bell, Pennsylvania) were placed under direct vision and positioned in the esophagus at the point where recorded end-expiratory pressure was lowest. The balloon contained 0.8 ml air. A separate catheter connected to suction was placed in the esophagus to keep it empty of air and liquid.[9]

After compliance and resistance were measured (see below), experimental asthma was induced according to the method of Gold et al.[10] Thirty micrograms ascaris protein in 10 ml H_2O were delivered over 10 minutes by an ultrasonic nebulizer (Mistogen model EN143A, Oakland, California) inserted between the anesthesia machine and the tracheostomy tube. Pulmonary resistance was measured at 5-minute intervals thereafter. The volatile anesthetic was started 10 minutes after the end of the aerosolized ascaris antigen administration in Group 1 dogs and immediately after the end of the ascaris antigen administration in Group 2 dogs. Ten breaths of 2.61% halothane or 6.6% enflurane were given followed by 0.87% halothane or 2.2% enflurane for the duration of the study. MAC for halothane in dogs is 0.87%[11] and for enflurane, 2.2%.[12] Intermittent thiopental was continued in the thiopental studies. No further thiopental was given to dogs receiving halothane or enflurane. Each dog was studied three times. Only one anesthetic was studied in a given dog on each day. At least one week elapsed between successive studies in any one animal.

Transpulmonary pressure was measured with a differential pressure transducer (PM 5T C, Statham Instruments) connected to the esophageal balloon and to a needle inserted into the tracheostomy tube. Airflow was measured with a Fleisch #1 pneumotachygraph head and pressure transducer (PM 97 TC, Statham Instruments). Pressure and flow signals were recorded with a Grass Model 5C recorder.

Dynamic lung compliance (C_L) was calculated by dividing tidal volume by pressure change measured between points of zero flow on the recording (fig 1). To measure pulmonary resistance (R_L), total transpulmonary pressure was measured at the point of maximum inspiratory flow. With the sinusoidal pattern used, this occurred exactly one-half way through the inspiratory cycle and corresponded to an inspiratory volume of 200 ml. Pulmonary elastic pressure (P_{el}) at this point was calculated by dividing 200 ml by compliance:

$$P_{el} = \frac{200 \text{ ml}}{C_L \text{ (ml/cm } H_2O)}$$

Pressure required to overcome flow resistance (P_{res}) was calculated by subtracting elastic pressure from total transpulmonary pressure. Pulmonary resistance (R_L) was then calculated by dividing P_{res} by instantaneous flow rate ($\dot{V}$) at this point:

$$R_L = \frac{P_{res}}{\dot{V}}$$

All volumes were corrected to BTPS. Pulmonary resistance was calculated at 5-minute intervals from a mean of 7 consecutive breaths.

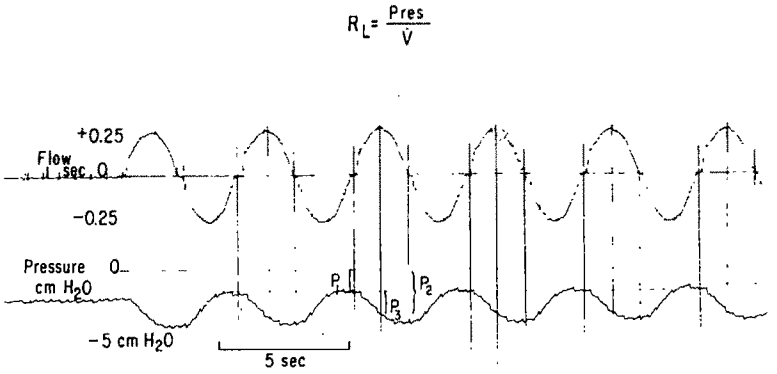


FIG 1. Pressure and flow recording obtained during study. Dynamic compliance is tidal volume (400 ml) divided by pressure difference between points of zero flow ($P_2 - P_1$). Resistance (R_L) was calculated when inspired volume ($\dot{V}$) was 200 ml by subtracting elastic pressure $\left(\frac{200}{CL}\right)$ from total pressure (P_3).

Pulmonary resistances 20 minutes after exposure to ascaris antigen were compared to each other and to lung resistance before inhalation of antigen by a two-way analysis of variance[13] and Student-Newman-Kuls test for multiple comparisons.[14] Lung compliances during each anesthetic were compared at 5-minute intervals by the same statistical analysis.[13,14] The level of statistical significance used was 0.05 throughout.

RESULTS

In the dogs in Group 1 (thiopental anesthesia), pulmonary resistance began to increase 15 minutes after administration of the aerosolyzed ascaris antigen was completed, peaked at 20 minutes, then gradually declined. Prior to administration of the ascaris antigen, pulmonary resistance averaged 1.86 ± 0.09 (mean ± SEM) cm H_2O/L/sec during thiopental anesthesia and was greatest 20 minutes (3.20 ± 0.04) after ascaris antigen administration, gradually returning to control levels by 35 minutes (fig 2). Inspired halothane 0.87% and inspired

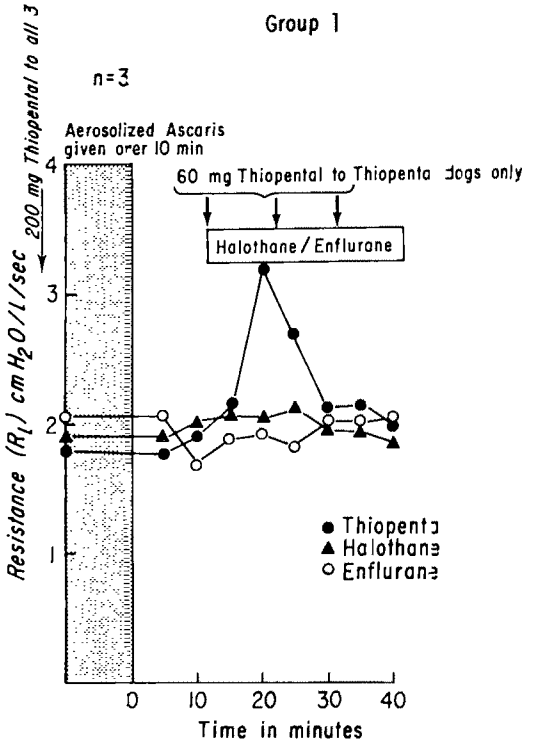


FIG 2. Changes in pulmonary resistance following 10 minutes of exposure to aerosolyzed ascaris antigen in three sensitized dogs during thiopental, halothane, or enflurane anesthesia. Halothane and enflurane limited the rise in resistance induced by ascaris antigen.

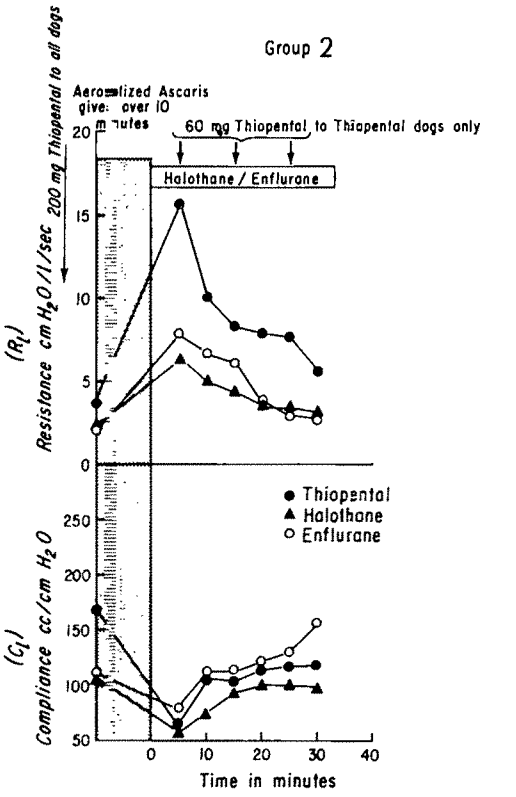


FIG 3. Changes in pulmonary resistance and compliance following 10 minutes of aerosolyzed ascaris antigen in 3 dogs during anesthesia with thiopental, halothane, or enflurane. These dogs were selected because they exhibited at least a 300% increase in pulmonary resistance when exposed to antigen during thiopental anesthesia. Both halothane and enflurane limited the rise in resistance induced by ascaris antigen. Compliance was not significantly different during thiopental, halothane, or enflurane anesthesia.

enflurane 2.2% limited this increase. Twenty minutes after completion of inhalation of ascaris antigen, pulmonary resistance was 2.17 ± 0.38 and 1.87 ± 0.32, respectively.

In Group 2 (the highly reactive dogs), pulmonary resistance was 3.57 ± 1.27 cm H_2O/L/sec prior to exposure to ascaris antigen. Five minutes after the completion of the antigen administration, pulmonary resistance rose to 15.6 ± 3.8, gradually decreasing to 8.2 ± 1.35 and 5.8 ± 0.95 at 20 and 25 minutes, respectively, during thiopental anesthesia (fig 3). With 0.87% halothane and 2.2% enflurane, pulmonary resistance was 4.20 ± 0.85 and 4.20 ± 0.56, respectively, 20 minutes after completion of the aerosolyzed antigen administration. In the 6 dog., 20 minutes after the end of antigen administration, pulmonary resistance was 5.72 ± 1.29 cm H_2O/L/sec during thiopental, 3.18 ± 0.62 during halothane, and

TABLE
Pulmonary Resistance (R_L) Prior to and 20 Minutes After Ascaris Antigen Administration

Dog	Thiopental (cm H_2O/ L/sec)	Thiopental + antigen (cm H_2O/ L/sec)	Halothane + antigen (cm H_2O/ L/sec)	Enflurane + antigen (cm H_2O/ L/sec)
1	1.9	3.5	1.6	1.5
2	1.2	2.4	2.0	1.6
3	2.0	3.7	2.9	2.5
4	2.0	7.7	5.2	3.1
5	1.9	6.2	2.5	4.6
6	5.1	10.8	4.9	4.9
Mean	2.35	5.72*	3.18	3.03
SD	1.38	3.16	1.51	1.46
SEM	0.56	1.29	0.62	0.60

*Pulmonary resistance was significantly greater following exposure to antigen during thiopental anesthesia than it was during thiopental anesthesia before exposure to antigen. It was also significantly greater following exposure to antigen during thiopental anesthesia than it was following exposure to antigen during halcthane or enflurane anesthesia.

3.03 ± 0.60 during enflurane (see table). Pulmonary resistances during halothane and enflurane anesthesia were significantly different from those observed during thiopental anesthesia at 0.05 level. Pulmonary resistance during enflurane was not significantly different from pulmonary resistance during halothane, nor from control levels of pulmonary resistance before exposure to antigen.

In Group 2 (the highly reactive dogs), pulmonary compliance during thiopental anesthesia was 174 ± 57 cc/cm H_2O prior to antigen administration. Compliance decreased to 62 ± 16 five minutes after completion of the aerosolyzed antigen and gradually increased to 124 ± 32 after 30 minutes in thiopental anesthetized dogs. In the dogs anesthetized with halothane, compliance decreased to 61 ± 14 cc/cm H_2O 5 minutes following antigen administration and gradually increased to 88 ± 14 at 30 minutes. In dogs anesthetized with enflurane, compliance decreased to 86 ± 28 5 minutes after antigen and gradually rose to 127 ± 38 30 minutes after administration of ascaris antigen (fig 3).

Compliance measurements 5 and 10 minutes after the end of ascaris administration were significantly different from preantigen controls at the 0.05 level with all three anesthetics. At each 5-minute interval, there was no significant difference in compliance during anesthesia with thiopental, halothane, or enflurane.

DISCUSSION

Hypersensitivity to ascaris antigen occurs in dogs as a result of a parasitic infection. Not all dogs react to the antigen. Dog No. 3 initially had a negative skin test to ascaris antigen and did not respond with an increase in lung resistance when challenged with ascaris antigen during thiopental anesthesia. After sensitization with 20 μg ascaris antigen biweekly for one month, pulmonary resistance increased from 2.0 to 3.7 cm H_2O/L/sec when exposed to aerosolyzed ascaris antigen.

Studies by Gold et al[10] indicate that dogs are suitable subjects for the study of experimental asthma. In the ascaris dog model, the physiologic and radiologic changes in allergic dogs are similar to changes observed in asthmatic human subjects.[10,15] Such animals exhibit a marked increase in pulmonary resistance when exposed to aerosolyzed antigen, an increase which is rapidly reversed by bronchodilators.[10] Tantalum bronchograms indicated that this response involves constriction of large and small airways.[16] Moreover, Gold et al have recently shown that asthma induced by ascaris antigen results in degranulation of mast cells with histamine release, as well as vagally mediated reflex bronchospasm.[17]

Pulmonary resistance varies inversely with lung volume, increasing as lung volume decreases.[18] In the present study, ventilation was controlled and all measurements were made at the same lung volume. It is possible that total lung volume differed slightly with the three anesthetics,[19] but it is unlikely that small changes in total lung volume could account for the large differences in lung resistance measured.

Changes in carbon dioxide are known to alter pulmonary resistance.[20] We did not measure arterial or end-tidal CO_2. We maintained tidal volume and respiratory rate at constant levels in each dog and with each anesthetic. It is possible that CO_2 production decreased as anesthetic depth increased. The maximum decrease that could have occurred in our study during halothane is 15%.[21] Therefore, arterial and alveolar CO_2 tensions could decrease to that extent at most. According to Ingram, the net effect

would be an increase in lung resistance.[20] In addition, Coon and Kampine have shown that 1 MAC enflurane and 1 MAC halothane block the bronchoconstrictor response to hypocapia.[22] Thus, the small change in alveolar CO_2 that may have occurred during halothane and enflurane anesthesia could not account for the decrease in pulmonary resistance seen during anesthesia with halothane and enflurane.

Pulmonary compliance in the dogs in Group 2 decreased following exposure to aerosolyzed ascaris antigen. The magnitude of the decrease was similar to that reported by Gold et al.[10] The dogs in our Group I similarly exhibited a decrease in compliance but because there was a great deal of scatter in the data, it did not attain statistical significance. The decreases in compliance could have been the result of atelectasis secondary to severe bronchoconstriction and airway closure. Alternatively, these changes could have been due to peripheral airway constriction caused either by the direct effect of chemical mediators[23] or reflex stimulation of vagus nerves[24] on small airway smooth muscle.

In conclusion, 0.87% halothane and 2.2% enflurane limited the increase in pulmonary resistance produced by aerosolyzed ascaris antigen in sensitized dogs. Enflurane may be a useful alternative to halothane in asthmatic patients.

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Pediatric Anesthesia in Perspective

Sixteenth Annual Baxter-Travenol Lecture

ROBERT M. SMITH, MD*

PEDIATRIC anesthesia has been in existence as a subspecialty for slightly over 30 years, dating back to the end of World War II.

It is time to look back, around, and ahead, to check the course that we have been following, and the direction in which we seem to be heading.

What I hope to do is to present a broad view of the field of pediatric anesthesia as it now stands, evaluate some of its accomplishments, sort out some of its weaknesses, look at portents of the future, and attempt to suggest paths that might be taken for further improvement of the services that this subspecialty might be able to supply.

There are many who will disagree with my opinions, especially among my younger associates, whose views I greatly respect. Nothing would please me more than to have present figures bettered, and to have my premonitions and warnings prove unwarranted.

Most observers would agree that on the surface of things, pediatric anesthesia has been progressing at an acceptable rate. In evaluating this progress, it is important to differentiate what is truly an improvement from something that is simply "new." There has been an inordinate emphasis on "what is new" in many fields of anesthesiology, often with little relation to the actual value of the particular items being introduced.

I believe that progress in pediatric anesthesia should be measured by definite criteria relating to both clinical and nonclinical aspects.

Extending the capability of the surgeon seems the reasonable measure of progress in clinical anesthesia. This would include enabling the surgeon to perform more extensive and more difficult procedures on sicker (and smaller) patients, at the same time reducing mortality and morbidity. Widening the sphere of surgical operations should occur with increasing availability of skilled pediatric anesthesiologists, allowing surgeons greater opportunity to operate in ambulatory surgical areas and in less specialized hospitals.

Both the care of awake patients and the reduction of suffering and emotional stress are definite measures of progress in our field.

Nonclinical criteria of progress in pediatric anesthesia should include the promotion of teaching and constructive investigation. Let us examine these developments more closely.

It is definitely in the clinical field that pediatric anesthesia has made its greatest progress, and this primarily by extending the capability of the surgeon. A backward glance will help evaluate progress in this area. Looking 'way back to 1912, one surgeon stated that any operation on a child that lasted more than 15 minutes was doomed to failure. Looking back to 1940 or 1950, where we place the beginning of pediatric anesthesia as a special field of endeavor, tentative beginnings had been made in pediatric surgery. The patent ductus arteriosus had been

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closed in healthy children of school age, and infants with tracheo-esophageal fistulae were the greatest challenge of that day, but only in major pediatric centers. In the outlying areas tonsillectomy, appendectomy, and fracture reduction made up the bulk of the surgery on children.

Improvements in the intervening years, definitely coming from a multitude of sources, now enable surgeons to operate for an hour or more inside the bloodless, still heart of a premature infant, to transplant kidneys in children with advanced renal failure, and to undertake 15-hour midface advancement procedures on children while ductus arteriosus, tracheo-esophageal fistula, and ureteral reflux operations are being performed in suburban hospitals.

The incidence of anesthetic mortality should be an essential measure of anesthetic excellence. Due to the difficulty in determining the true cause of operative death, reliable statistics have been hard to produce. Earlier estimates, based on the study of Beecher and Todd,[1] and others, placed the incidence of anesthetic death in adults at 1/1500, while the incidence of anesthetic death in children under 10 years old was generally believed to be considerably higher, and children within this age group were widely considered to represent increased anesthetic risk (table 1). For many years, this concept was used as an excuse for complications and deaths that should have been avoided. While it is still difficult to obtain accurate statistics and definite causes of death, it has been possible to produce enough evidence to correct the idea that pediatric patients present increased risk.

The concept that all children under 10 carried increased anesthetic risk was altered first when it was shown that 90% of the operative mortality occurred during the first 6 months of life. We know now that normal children between 1 and 10 years of age should have higher expectation of surviving anesthesia than patients of all other ages. The second phase in correcting this concept is now under way. Mortality in infant surgery has been reduced to such an extent that operations previously postponed until children were 3 or 4 years old are being performed nearer and nearer to the neonatal stage, and many of those operations that are mandatory at birth are now being performed with remarkable success.

This I believe is a major advance. Our evidence consists of large numbers of procedures of similar type in which there have been no deaths of any kind. The record of the Pittsburgh Eye and Ear Infirmary,[2] in which 37,000 children underwent tonsillectomy without a death, is an example. At the Philadelphia Children's Hospital 50 infants with uncomplicated tracheo-esophageal fistulae have been operated upon without any deaths.[3] In such statistics there is no possibility of shifting of blame, or juggling of figures.

In surveying the total experience where deaths have occurred, an extremely thorough study must be made to produce reliable figures. Such a study has recently been reported by Elwyn[4] in an inclusive series of all children who received anesthesia at the Primary Children's Medical Center in Salt Lake City from 1970 to 1975. The record of 1 anesthetic death in 29,000 pediatric anesthetics stands as an excellent achievement. While such records cannot be regarded as standards that all should be expected to maintain, it is hoped that such figures will be used in the future in determining who should administer anesthesia to children, where surgery should be performed, and what allowances, if any, should be made if unexplained operative deaths occur in infants and children.

TABLE 1
Mortality in Pediatric Anesthesia and Surgery

Previously Established Concepts (1955)	
Adults: Incidence of anesthetic mortality	1/1500
Children (0-10 yrs): Various figures, higher incidence	1/1000±
Statistics Now Available (1978)	
Tonsillectomy: 37,000 cases (Pittsburgh)	No deaths
Neonates: 50 uncomplicated tracheoesophageal fistulae (Philadelphia)	No deaths
All types: 29,000 procedures, 1970-1975 (Utah)	1 anesthetic death

The reduction of mortality and other anesthetic complications has brought several changes. It has enabled surgeons to perform operations in other than pediatric centers (a questionable contribution), and to institute outpatient surgery on a far more extensive scale—in most cases a very definite advantage for child, parents, parking, and pocketbook.

It would seem reasonable to determine what major factors contributed to the pronounced gains in pediatric anesthesia. It is impossible to name all, for there have been many, and they have been derived from many sources, both inside and outside the field itself. Contributions in technical details of pediatric anesthesia include those of equipment, agents, anesthetic technics, and supportive care, as well as improvements in surgery and contributions from other fields.

Among the improvements in equipment have been masks, endotracheal tubes, airways, laryngoscopes, and anesthesia machines, most of which originated in adult anesthesia. The elimination of the frightening black rubber mask, and its replacement by lightweight plastic masks and breathing tubes, have been particularly valuable, being far less objectionable to the child, and, by reason of their transparency, reducing the danger of aspiration.

The improvement in anesthetic agents has been of great importance. Of those used in 1940—diethyl ether, divinyl ether, tribromoethanol, cyclopropane, and N_2O—only N_2O and local anesthesia survive. The elimination of explosive agents, particularly ether—for years the undisputed mainstay of pediatric anesthesia—and its replacement by halothane has proved to be one of the greatest advances in our field, enabling us to set aside the confusion of rational and irrational precautionary measures, but of greater importance, allowing free use of electric surgical and monitoring devices. The use of cautery has been of unexpected value, reducing blood loss, in our experience, by as much as 80% in many cases. Unfortunately, there has not been a parallel reduction in operating time, surgeons showing increasing disregard of the passage of time in the operating room. While this may reflect increased confidence in anesthesia, the situation in many teaching hospitals has reached dangerous proportions.

Additional advantages in the elimination of ether have been marked reduction in postoperative nausea and faster return of full consciousness, major factors in developing the outpatient surgery of today. The elimination of ether introduced a major change in underlying concepts. The explosive potential of ether formerly was overlooked in view of the fact that ether was the only agent that supported respiration, the quality of respiration at that time serving as the most reliable guide to anesthetic depth.

The situation now is reversed. Today any inflammable agent is considered obsolete, and stimulation of respiration is of little importance because ventilation is usually either assisted or controlled.

Out of this change has come a still greater departure from tradition. Endless effort had been spent in studying methods of avoiding dead-space and resistance in fashioning breathing equipment, for these are the factors that lead to increased work of breathing. With general abandonment of spontaneous respiration, ventilation by passive control is assured, and the work of breathing is eliminated, or at least reduced to inconsequential proportions. Instead of concentrating on maintaining the largest possible airway, we now insist upon using equipment that avoids distention or pressure, preferring instead to maintain a slight leak around the endotracheal tube to minimize the possibility of trauma.

The replacement of ether by halothane was momentous, and of more revolutionary nature in pediatric than in adult age groups; however, it did not produce the marked resistance occasioned by the introduction of endotracheal intubation or the use of muscle relaxants in infants and children. Many surgeons took strong stands against both of these innovations, and for years these methods were looked upon with disfavor, and blamed for numerous complications. The current unquestioned acceptance of the anesthesiologist's choice of agent and technic by surgeons is a far cry from the situation of the 1940's and 1950's, when the surgeons still felt it their prerogative and responsibility to have a major voice in the management of anesthesia. The agents generally used and our technics for using them now seem to be established on fairly firm ground. There appear to be several methods of managing almost any patient, and we seldom insist that there is only one correct way to approach a given situation.

Halothane leads all other agents for use in pediatric patients, but is supported by thiopental, muscle relaxants, N_2O, ketamine,

IV narcotics, and local anesthetics, providing combinations applicable for most of the surgical procedures now undertaken. Thus, the need for better anesthetics does not appear to be immediate or urgent, even though present agents are still not perfect, and the search for the ideal agent continues. The danger of halothane hepatotoxicity, if existent at all, is believed to be less in children than in adults. This belief was strengthened by a survey of 1,500,000 patients under 21 years of age who were anesthetized with halothane. There were 15 deaths in which halothane was involved but only 5 in which halothane was the principal suspect, and only 2 of these were prepubertal.[5]

The use of muscle relaxants is widely accepted. The several complicating actions of succinylcholine are well documented, while the nondepolarizing relaxants stand among the most reliable and predictable drugs in our practice. In spite of the numerous conflicting studies of drug tolerance and intolerance, clinical use of all muscle relaxants follows relatively standard lines, and dosages, though altered slightly by personal biases, tend to agree rather closely. Table 2 shows dosages of relaxants commonly used, to which I have added my own adaptation of the dosage of succinylcholine for intubation of small infants. Instead of giving enough to cause apnea, with the attendant risk of hypoxia, the use of a subapneic dose, approximately 1 mg/kg of succinylcholine given IM, allows continuous, adequate ventilation, but reduces the infant's activity enough to make intubation relatively simple.

There has been continual change in anesthetic technics. Open-drop administration was discarded with the elimination of ether, all other agents requiring technics affording ventilatory assistance. The variety of closed and semiclosed technics, nonrebreathing valves, and the endless variations on the T-tube have resulted in volumes of papers and barrels of discarded devices. To the simple T-tube one now adds expiratory limb of specific dimensions, bag, valve (optional), heating and humidifying adaptations, and scavenging device! While this appears confusing to the novice, application is not difficult; and we feel that technics as well as agents are reliable, practical, and adequate for the present time.

There has been increasing interest in the field of monitors in all branches of anesthesia. The remarkable progress that already has taken place probably represents the mere beginning of a rapidly accelerating surge of instrumentation. In comparison to the relatively stable position of agents and technics in pediatric anesthesia, the whole situation in relation to monitors is widely varied, highly dynamic, and actively disputed.

The word "monitor," generally used to denote an instrument in our application, literally means a guardian or watcher. It is important to remember that we are endowed with several extremely valuable monitoring devices that frequently are overlooked. These are the eyes, ears, and fingers, which, acting as sensors, and filtered through the brain, as computer, provide continuous information of inestimable value (table 3). It should be emphasized that in pediatric anesthesia it is absolutely essential for the anesthesiologist to observe the operation continuously, with complete knowledge of

TABLE 3
Monitoring Methods: Basic Monitors

Eyes		Anesthesia chart
Ears	+	Stethoscope
Fingers		Blood pressure
		Temperature

TABLE 2
Pediatric Use of Muscle Relaxants

Agent	Intubation	Supplementation
Succinylcholine		
Standard dosage	1 mg/kg IV (2 IM)	. . .
subapneic dose	1 mg/kg IM	. . .
d-Tubocurarine	0.5 mg/kg IV	0.3 mg/kg IV
Metubine (1/2 dtc)	0.25 mg/kg IV	0.15 mg/kg IV
Pancuronium (1/5 dtc)	0.1 mg/kg IV	0.06 mg/kg IV

what the surgeon is doing, how the child is reacting, and what problems are being encountered. In the same vein, it is of utmost importance for anesthesiologist and surgeon to work together, to communicate freely, and to each be cognizant of the other's plan of action. One of the most valuable advances in pediatric anesthesia has been the very close relationship and mutual respect between anesthesiologist and surgeon, and the elimination of the rather stupid antagonism that once was nurtured in many institutions.

The major interest in monitors today is directed toward instrumental devices of increasing sophistication and of disputed indication. There are four basic monitors, however, which now are widely considered to be indicated for all pediatric anesthesia. It might be said with reason that the establishment of routine use of these monitors has been the most valuable of all advances in our field.

If used properly, the anesthesia chart serves as a basic monitor. Proper use means that documentation is started before the anesthesia is begun, and the responses to induction are measured and recorded. A thorough chart should show gradual, as well as abrupt, changes, which might not be recognizable unless visibly displayed. The value of the anesthesia chart should be considerably enhanced when automatic recording of trends in body functions becomes available in the near future. The chart is listed first, not because it is most important, but because it should come into play first, in the course of the anesthetic procedure.

The first instrumental monitor to be applied in the field of pediatric anesthesia, the precordial (or esophageal) stethoscope, has become—rightfully, I believe—the mark of the pediatric anesthesiologist, without which no anesthetic should be undertaken regardless of the presence of more advanced electronic instruments. The precordial stethoscope is one of the few major advances that originated within the field of pediatric anesthesia, and was subsequently adopted for use in adult anesthesia, in contrast to most other innovations, which have been brought into our field after prior development in other areas.

For many years after the measurement of arterial blood pressure had become routine in adult anesthesia, it was regarded as of slight importance in the anesthetic management of children, and impossible in infant management. The development of accurate, noninvasive methods of arterial blood pressure determination in infants and children of all ages has been of great significance, and the alterations observed in infants have been found to be more informative than those of any other age group. Safety, simplicity, and practicality give the blood pressure cuff unchallenged position next to the stethoscope as a standard, mandatory monitor for pediatric anesthesia.

The fourth monitor of standard use is the thermometer. It is less reliable, less foolproof, and less mandatory than the stethoscope and blood pressure cuff, but is now accepted as one of the essential devices.

The additional monitors being used in pediatric anesthesia appear to be of more importance under special indications (table 4).

Monitors seem to cast a spell over many of us, particularly the younger members of our specialty. I am convinced that younger individuals, who have not become familiar with physical signs and have natural facility with instruments, have a tendency to turn to the instruments too quickly, and use them more often than necessary, while older individuals, who are accustomed to getting along without and have less skill with in-

TABLE 4
Monitoring Methods: Supplementary Monitors and Measurements

1. Fluids given, urine output	9 Electrocardiograph
2. Measured blood loss	10. Central venous pressure
3. Venous pH, P_{CO_2}	11. Nerve stimulator
4. Arterial P_{O_2}, P_{CO_2}	12. Cardiac output
5. Inspired O_2 concentration	13. Right and left atrial pressures
6. End-expired CO_2	14. Serum Na, K, Ca^{++}, protein
7. Anesthetic vapor concentration	15. Serial hematocrit
8. Tssue O_2, CO_2	16. Coagulogram

struments, hesitate too long to take advantage of the help that monitors can provide. How fortunate to be exactly 40 years old!

Among measurements currently made, whether by instrument or other means, blood-gas determinations are among the foremost; and the availability of accurate blood-gas determinations on a 24-hour basis has become another essential in a properly equipped operating room. Measurement of blood loss, urine output, and central venous pressure follows practical indications, that of central venous pressure providing less reliable information in smaller children, and being essential only in more extensive procedures or during operations on particularly poor-risk patients.

The electrocardiograph, contrary to the opinion of many, I believe is of little value in uncomplicated procedures on normal children. The cardiac irregularities seen in children seldom appear to be of significance and are more apt to upset and distract the anesthesiologist than to harm the child. I am sorry to see the spreading tendency to drape an anxious child with paste, wire, and electrodes before starting a tonsillectomy. It has been argued that one should use all the safeguards available when anesthetizing a child, but if one considers the rapidly growing list of so-called safeguards, it is obvious that the line must be drawn somewhere (before the bottom of the list), and while there may be definite indication for the use of each, the needless use of any imposes more burden than safeguard. One does not put overshoes on a duck.

Rather than describing the use of each monitor, I should like to point out a few of the disadvantages that should be considered before one reaches for the switch (table 5). Some, such as the loss of a hand or foot, are all too obvious, but others, such as the added exposure of an infant during preoperative instrumentation, or the distraction of the anesthesiologist's attention during operation, are less commonly appreciated. The fact that the use of many monitors is complicated and requires practice and skill means that to be prepared to use them with accuracy on sick patients, one may have to learn on patients who would not ordinarily require their use. When this involves the manipulation of invasive devices, it presents a definite problem in ethics.

One of the most objectionable effects of monitoring the postoperative infant or child is seen in the absolute and prolonged immobilization that frequently is involved. It imposes a hardship for the child to endure and provides an open invitation for vascular stasis and ventilatory problems.

In spite of their disadvantages, monitors are of tremendous value in measuring the condition of the patient and guiding therapy. For best development of their potentiality, it is important to know what to look for in their adaptation for pediatric use. Desired features (table 6) include the obvious bids for safety, simplicity, and easy serviceability. Features less frequently stressed are widely observable signals and alarms. Many currently popular monitors, including the stethoscope and thermometer, are designed for use of the anesthesiologist only. Too many times there has been a bout of asystole or a sudden rise in temperature that has gone unnoticed for a critical lapse of time because the single listening-post was not being manned, whereas a generally audible alarm would have demanded immediate response.

We expect much more help from monitors in the future in evaluation of tissue and fluid

TABLE 5
Disadvantages and Potential Dangers of Monitoring Devices

Exposure of child	Long-term immobilization of child
Alarm, pain in establishment	Interruption of rest
Delay in starting operation	Mechanical breakdown, monitor error
Injury:	Distraction of anesthesiologist's attention
Nasal, urethral, rectal trauma	Practice required to develop skill needed for critically ill
Tracheitis, esophageal perforation	
Tissue injury, blood loss	
Vascular irritation, embolus	
Loss of digits, extremity, or life	
Burns (heat, electric)	

TABLE 6
Monitors: Desired Features and Measurements Needed

Desired features	Measurements needed
Practical	Consciousness
Reliable	Pain
Accurate	Tissue oxygenation
Noninvasive	Blood volume
Signals widely observed	Cardiac output
Alarms widely observed	Pulmonary vascular resistance
Stable, durable	Intracranial pressure
Easily serviced, adjusted	
Simple	
Inexpensive	

metabolism and numerous aspects of cardiac, respiratory, and renal function. A particular need is the ability to evaluate consciousness and the sensation of pain. The inability to recognize these two components in paralyzed patients stands as a major deficiency in the practice of anesthesiology.

Another area where major advances have been made is that of patient support. Supportive care has played an increasingly important role in the successful outcome of pediatric operations, sicker and smaller patients depending more and more upon this factor. In many situations, prevention of intercurrent infection in handling neonates and maintenance of body temperature have become of greater concern than administration of anesthesia.

Better understanding of the infant's mechanism of temperature control has taught us that conservation of body heat is more important than application of external heat. Warm operating rooms and maximal covering of body, limbs, and head have been found to be most essential. Heating lamps are valuable as the operation is getting underway, water blankets now being regarded as of secondary importance.

It was most fortunate for pediatric surgery that antibiotic therapy entered the picture at precisely the same time that many of the more heroic operations were first attempted, saving the lives of innumerable puny infants who would otherwise have been victims of postoperative infection.

Although we still fuss about IV fluid therapy, great strides have been made in both the technic and management of this fundamental feature. The development of the present IV infusion apparatus was one of the most difficult and drawn-out problems of pediatric care, our first sets having consisted of an open-topped beaker with rubber tubing and a side-armed syringe fixed to the end. Intravenous fluids in infants were limited to dextrose and water, in minimal amounts, but proved adequate due to more generous use of whole blood.

The "dry" regime of IV fluid therapy continued to dominate the scene for two decades, but recently has been threatened by the aggressive concept of abundant hydration. For infants who have passed the first 10 days of life, there has been wide acceptance of the guide established by Holliday and Segar (1957),[6] based on rate of metabolic activity adapted to weight (table 7). The major difference of opinion has been confined chiefly to management of the neonate, whom the "dries" prefer to maintain with 0 to 4 ml/kg/hr, while the "hydraters," following the theory of Shires,[7] go as high as 25 ml/kg/hr.

In this situation, it seems that both concepts make the same mistake of suggesting one line of treatment for all patients. It seems far more rational to consider each neonate individually, as in table 8, for it becomes evident that the infant in danger

TABLE 7
Intravenous Fluid Therapy Operative Support, Infants and Children[6]

Weight (kg)	Amount (ml/kg/hr)
0 - 10	4
10 - 20	40 + 2 for each kg over 10
Over 20	60 + 1 for each kg over 20

TABLE 8
Intravenous Fluid Allowance for Neonates (0 to 10 Days)

Dry concept	Hydration concept (Shire.)
0 - 4 ml/kg/hr	15 - 25 ml/kg/hr
Individualization concept (ml/kg/hr)	
Cardiac, neurosurgical	2
Hernia, harelip	4
Intestinal obstruction	6 - 8
Gastroschisis	8 - 10
Necrotizing enterocolitis	15 - 20

of cardiac failure should be limited to a minimal amount of fluid, while others having normal water turnover or enjoying wider margins of error deserve increasing amounts, normal being considered 4 ml/kg/hr while allowances of 6, 10, and 15 to 20 ml/kg/hr have been found appropriate for infants with increasing fluid demands, such as those with intestinal obstruction, gastroschisis, or necrotizing enterocolitis. In all situations reliance must be placed upon frequent evaluation of signs rather than upon use of any preset rules or formulae.

Another step of great importance has been the development of the team concept in management of pediatric surgical patients. The early advances in pediatric surgery were credited almost entirely to the surgeons, with good reason. The value of anesthetic management next became evident. The development of recovery room care, and later the intensive therapy and respiratory therapy adjuncts, as well as experienced special nurses for continued care of infants following repair of tracheo-esophageal fistulae and similar lesions, all these combined to make an interlocking team in which all members were invaluable.

The importance of postoperative nursing care becomes particularly evident when pediatric surgery is attempted in general and suburban hospitals. Frequently it is possible to find surgeons and anesthesiologists of sufficient skill to bring infants through standard operations in these locations, but experienced nursing personnel is apt to be lacking. Unless an anesthesiologist is certain that expert aftercare is available for his patient, he may face the choice of staying with the child himself or advising transportation of the child to a more suitably equipped hospital.

The development of ventilatory therapy has been slow and arduous but has finally reached a stage of considerable finesse. The recent introduction of intermittent mandatory ventilation (IMV) as a means for the gradual termination of controlled respiration solves one difficult problem, but leaves another, the endotracheal tube itself, which seems to be both the lifeline and the danger point of infant support.

The addition of total parenteral alimentation in the postoperative care of small infants has resulted in marked reduction of surgical mortality. It has been of particular value in sustaining infants following reduction of intestinal obstruction. Ten to twenty days of IV support may be required before return of normal gastrointestinal function. Formerly many of these infants died of inanition and peritonitis. With parenteral alimentation, however, similar infants can be maintained in normal nutritional balance and death rarely occurs.

Of the many advances in surgical technic that have helped the progress of pediatric anesthesia, the mesh closure of omphalocele and gastroschisis has been outstanding, for it has eliminated the hazards associated with forcing the viscera into the inadequate peritoneal cavity.

Enough has been said of the accomplishments. Now it is time to look at a few of the weaknesses and failures related to pediatric anesthesia.

One of my first statements was that there might be some misdirection in the work of the pediatric anesthesiologist. I was referring to the tremendous effort expended by all members of our teams in attempts to prolong the lives of patients who had no chance of surviving more than a few days, or else were so severely handicapped that life could only be a burden for the patients and all concerned with their physical or economic care.

When an anencephalic monster is born, it is not allowed to survive. There have been attempts to persuade parents to refuse operation on infants with other overwhelming congenital anomalies, but these have had disappointing results. As shown in a recent survey by Todres and associates (1977),[8] there are so many complicating factors, including the possibility of finding new forms of treatment, guilt complexes, religious and racial restraints, and marital stresses, that little agreement is possible as to how to

regulate such problems. We are left in a position where we blindly strive for the survival of all living creatures, regardless of eugenics or economy. We spend millions on open-heart repair in children with Down's syndrome, and race to the bedside of moribund infants every time they get into trouble. It would seem more constructive if we could spend greater effort on delivering superior care to children with high potential and reduce the excessive expenditure of time and personnel on the moribund, the totally demented, and the neonate with high thoracic meningocele and quadriplegia.

One of the advances previously mentioned was improved availability of pediatric anesthesiologists. This is only a half-truth. In spite of a numerical increase in our number, the demand still far exceeds the supply, and many posts have gone unfilled for several years. Lack of interest in this most pleasant and rewarding field is hard to explain, but reflects upon those of us who have been unsuccessful in stimulating enthusiasm for our special area.

In our technical practices we have problems in nearly every aspect, including preoperative medication, induction, airway control, monitoring, and fluid therapy, as already mentioned. There are at present three problems that appear to be particularly important and deserve special emphasis. These are the questions of how much oxygen to administer to premature infants during surgery, the hazard of airway management, and the management of anxiety and suffering in the awake child.

Due to the increasing rate of survival of premature infants, the number of these scrawny patients coming to operation is steadily climbing. It is estimated that one-third of these infants have inguinal hernia, and our experience centainly bears this out. Experience with premature infants has brought us face-to-face with one of our greatest dilemmas — the problem of how much oxygen to allow them before, during, and after operation.

All premature infants, and many small neonates, bear the double danger of developing respiratory distress syndrome (RDS) and retrolental fibroplasia (RLF). Infants with RDS may require very high concentrations of oxygen to avoid hypoxic brain damage. On the other hand, there are many infants who, if given even slightly increased amounts of oxygen, will develop atelectasis, pulmonary irritation, and partial or total blindness. Our inability to determine the correct concentration of oxygen to give the individual infant keeps many in a zone of uncertainty for several weeks after birth. The problem is especially difficult because there is no safe area for all, for infants with RDS can become hypoxic while breathing 80% O_2, while RLF can develop in other infants breathing 25 to 30% O_2, and has been reported even in infants with tetralogy of Fallot, who presumably were hypoxic from birth. The use of air or nitrogen as a diluent for oxygen is now an accepted practice, but estimation of gas flows actually needed requires monitoring of arterial oxygen above and below the union of ductus arteriosus and aorta, and the level of tissue oxygenation.

A serious problem in pediatric patients of all ages is that of the airway, truly the focal point of the child's struggle for life. At present it appears that this problem is increasing rather than decreasing. In the operating room we have difficulty with obstruction during induction, and severe spasm on recovery. Intubation and extubation of the trachea are well known as the two greatest trouble sites in the course of the entire anesthetic procedure. The unfamiliarity of inexperienced anesthetists with the anatomy of normal infants and children leads to many preventable complications, while the high incidence of pathology in and about the airways of infants and children presents a continuing challenge to the most experienced. Tumors about the mouth, cystic hygroma, choanal atresia, Pierre-Robin syndrome, cleft lip and palate, Treacher-Collins syndrome, craniofacial synostosis (Apert's and Crouzons' syndromes), and Hunter-Hurler's syndromes appear in the varied and continuing daily parade of pathology, while foreign bodies, fractures, and infections may be counted upon to enliven evenings and weekends.

We appear to have passed the most intense phase of our involvement in the emergency treatment of asthma. The management of epiglottitis and laryngotracheitis now presents the most critical need of acute airway care. The responsibility for definitive management of these patients has quite appropriately been turned over to pediatric anesthesiologists, who thus far appear to have handled the precarious situation with surprising success.

A particularly disturbing development is now seen in the growing incidence of tracheal stenosis and upper airway damage following treatment in pediatric treatment rooms, emergency areas, intensive care units, and especially in long-term management of infants in neonatology units.

In many situations this seems to stem from the fact that trained anesthesiologists are no longer being called upon to manage airway problems in these areas but have been replaced by individuals lacking experience in airway management. Problems of endotracheal intubation now appear to be a popular topic in pediatric journals. One article recently was concerned with an infant who had been intubated (and reintubated) 329 times during treatment for respiratory distress syndrome. Another told of an infant whose esophagus had been perforated during attempts to intubate the trachea.[10]

While these particular complications probably should not be blamed on anesthesiologists, they may be considered evidence that we have not been successful in establishing the importance of airway management among our medical colleagues. This is nowhere more apparent than in the approach to tracheal intubation in some neonatology units, where medical students are allowed repeated attempts at intubation of premature infants, followed by further attempts by first-year medical residents, and then on up through gradually decreasing levels of inexperience, the gradation between bottom and top sometimes being less than impressive.

The development of subglottic scarring and stenosis, whether produced by anesthesiologist or untrained personnel, threatens to be one of the most-to-be-feared of the nonfatal complications that we encounter. The greater incidence of subglottic stenosis following intubation for the relatively unexciting laryngotracheobronchitis, or croup, has made treatment of this disease of more concern than that of epiglottitis, for which we now intubate without hesitation, experience having taught us that extubation can be expected within 48 to 72 hours, after which there will be full recovery with no complications.

The third weakness, or, in this instance, frank failure, is neither life threatening nor scientific in nature, which may give some explanation for its existence. This is our failure to reduce the suffering of sick children, to appreciate their anxieties, or to answer many of their calls for help.

Rather than keeping abreast of the progress in other aspects of patient care, we have allowed a gap to develop and enlarge between methods of treatment and the various forms of distress, a few of which are listed in table 9. We are cognizant of the pain of needles, but make slight attempt to avoid their use when there are reasonable alternatives, often using a larger needle than necessary. Among the unpleasant experiences that appear most objectionable at the time are nasotracheal suction, prolonged ventilatory support, and the pain of awakening with tight casts compressing sensitive wounds. In follow-up studies, however, the remembrance of pain is reported less than the anguish of separation from parents, which appears to hurt after the wounds are healed. In the operating and recovery rooms, one certainly hears more cries for parents than cries of pain. This is not tissue

TABLE 9
Distressing Experiences of Hospitalized Children

Physical pain	Emotional stress
Needles, dressings, wounds	Separation from parents
Discomfort	Unpleasant smells, tastes
Dizziness, nausea	Vomitus, dressings
Examinations	Medicines, anesthetics
Restraints	Unpleasant sounds
Casts, traction	Screaming patients
Drainage (chest, nasogastric, urethral) cannulae, infusion	Clattering instruments
Nasotracheal suction	Disturbing sights
Prolonged intubation, tracheostomy	Bleeding, disfigured, crippled, comatose, moribund, and "cardiac arrest" patients
Mechanical ventilators	Masked, gowned personnel

pathology, but is suffering, which leaves lasting effect, and which we obviously are not handling effectively.

Many children coming to the operating room for the first time suffer from fear of the unknown; others have established fears suggested by friends, books, or television. Adolescents have been reading "Coma" and are afraid that their bodies will be stored for future use of spare parts. One television program recently portrayed a patient dying from halothane hepatotoxicity, complete with futile cardiac massage.

Parents communicate concern to their children. It has been surprising to find that 90% of the parents who wish to be with their children prior to anesthesia are parents of children coming for tonsillectomy or hernia repair while children about to have cardiac or other extensive procedures usually come unattended. We believe that this has been due to greater effort to orient cardiac and orthopedic patients and parents, who have had considerable contact with hospital and personnel long before the operation.

In 1938 Ralph Waters wrote one of the first articles on pediatric premedication, suggesting morphine and scopolamine.[11] In spite of the fact that more has been written about premedication than any other phase of pediatric anesthesia, very little progress has been made in the intervening 40 years. Innumerable agents and combinations have been tried, usually on an unsound investigative basis, with 60 to 70% success, the remainder being over- or undersedated. The logic of sedation has been irrational, since dosage has been chosen by the child's weight or age, rather than by the degree of his anxiety. A lethargic, fat 4-year-old, by such standard, might receive twice the dose of an anxious, scrawny, hyperactive child who is literally climbing the walls.

Agents used for sedation are less than predictable, the much advertised tranquilizing agents proving less reliable than barbiturates, with great variability in patient response and a number of side effects, diazepam producing apnea, hydroxyzine producing fever, and compazine producing hypotension. Our traditional method of injecting sedatives by needle gives rise to some of the child's most lasting impressions of hospital life, and the dry, sour mouth caused by atropine is an added and entirely unnecessary discomfort for the waiting, hungry child.

Our lack of success in sedating pediatric patients is demonstrated by the wide divergence of approaches currently employed. These include heavy sedation, aiming at having all children asleep prior to anesthetic induction; light sedation, to provide a quiet, but not necessarily sleeping child; and no sedation, relying on informal play areas and personnel to fortify and distract the child's attention until it is their turn to be spirited away into the operating room.

While each of these approaches has certain advantages, none can be used for all children. We seldom take into account the fact that a child's anxiety varies with his age, his disease, the number of previous operations, type of parent, and other factors, and must be considered on an individual basis, one child of high anxiety level needing 2 to 3 times the usual sedative dose, while another child might need none. It is no wonder that we score poorly in controlling children's emotions.

Faced with these problems, our best approach would appear to be to attempt more rational use of presently available drugs, and continue the search for better sedatives, but of more importance, reduce our reliance upon use of sedatives by putting more effort into controlling children's anxieties by more personal contact with the children and their parents.

When sedatives are employed, the first rational steps in their use would include elimination of needles, delaying use of atropine until the child is asleep, and greater individualization of dosage in relation to level of anxiety.

Of the agents currently used, pentobarbital appears more predictable than most, and without dangerous side effects. The excitement often seen with pentobarbital is not remembered by the child, and does not contribute to postanesthetic anxieties. It does not require injection. Average dosages are shown in table 10.

Morphine continues to be the best sedative agent for children. Narcotics are actually safer than many sedatives, for narcotics can be reversed quite effectively, whereas there is no way to control the action of most sedatives currently used. The easiest improvement to carry out among the many inadequacies related to preoperative sedation is the elimination of the dry mouth that follows atropine. This is possible either by delaying use of atropine until the child is asleep, or doing away with it entirely.

TABLE 10
Premedication: Sedation Without Depression

1. Avoid needles 2. Avoid dry mouth 3. Individualize dosage

Pentobarbital (Nembutal®)
Standard dose: 4 mg/kg. po or pr (max dose 120 mg).
Recommended dose (Smith): 0, ½, 1, or 2x standard dose as needed.
Give 45 min before early case, 2-3 hr before late case.
Repeat in 1 hr if necessary.

Morphine: 0.1 mg/kg SC, if indicated, 45 min preop.
Atropine: 0.1-0.4 mg IV or IM, after child is asleep.

The increasing desire of parents to be with their children at all times and to come to, and even into, the operating room with their children has further complicated the preoperative management of children. Many of these parents, highly emotional themselves, continually communicate their anxiety to their children, actually preventing them from settling down by constant attention and fondling. After bidding tearful last farewells as the child is wheeled off for his tonsillectomy, the parents may believe that they have kept faith with their child by staying with him until the last, but they actually have added considerably to his emotional stress.

If all parents who wish to stay with their children could learn to sit quietly beside the child's bed as sedation takes effect, and withdraw before the child is taken to the operating room, they would be justified in feeling that they had been of some help. Many pediatric anesthesiologists have yet to learn that the parent often needs more moral support than the child, and that attempts to gain the child's confidence are useless unless the parent's confidence has already been won.

Finally, what can be said about the future of pediatric anesthesia? This is a difficult question. Both pediatricians and pediatric surgeons are concerned about the survival of their specialties. Whatever their fate, that of pediatric anesthesia is sure to be at least as dark.

The reason for the concern lies in a combination of factors. The birth rate is declining at an easily perceptible rate. Improved health care and preventive medicine should curtail the incidence of many surgical lesions occurring in infants and children. Surgery of congenital cardiac defects is believed to have peaked already.

Of considerably greater effect on the growth of pediatric surgery and anesthesia is the dilution of patient care. With the continual training of more pediatric surgeons, many must move away from original teaching centers and set up practices at outside, or suburban, hospitals where they perform many of the operations previously restricted to the centers. With increasing numbers of surgeons and decreasing numbers of infants, such dilution will, and already has, so reduced the numbers of operations on small infants that there is inadequate teaching material either for the training of the inexperienced or for maintenance of skill of those previously trained in either surgery or anesthesiology.

Surgeons have already taken steps to limit the number entering training each year, but the main hope for surgeons and anesthesiologists lies in the development of centers properly distributed about the nation, and referral of patients to these areas by highly organized systems of triage and transportation. Neonatologists, feeling the same concern, have made successful strides to concentrate their efforts, but surgeons have not been able to promote the system as yet, and anesthesiologists have not entered the contest.

Important economic factors affect both the tendency to dilute and the tendency to centralize our practice. Patients are drawn to outlying hospitals by surgeons working outside the cities, and by reduced costs of hospitalization. For the smaller hospitals, adequate facilities for specialized pediatric surgery impose increasing financial burdens which the hospitals cannot afford and the government refuses to subsidize. Although this should send patients back to the center hospitals, centralization has not started to show the strength required to ensure the survival of our practice.

It is interesting to try to picture the type of pediatric surgery that lies ahead. There is obvious advantage in correcting deformi-

ties as early as possible, whether they require cardiac, orthopedic, general, genitourinary, or plastic procedures. Although the total number of infants born will decrease, the higher incidence of premature babies will probably result in an increased incidence of those born with defects.

Undoubtedly one will see not only more complicated operations being performed, but also an increase in the frequency with which they are performed. Transplantation of heart, lungs, and other organs should be standardized, as well as replacement of bones, joints, and muscles in treatment of tumors and major injuries. Surgery for correction of metabolic diseases, now in its infancy, should develop in the near future, and involve new physiologic problems for the anesthesiologist.

Among many procedures of the future, reestablishment of the patency of the trachea, whether by graft, reimplant, or other means, looms as one of the most urgent needs, and one that will require considerable input on the part of the anesthesiologist both in the initial procedure and in the aftercare of the child. With such goals to anticipate, it is definitely to be hoped that pediatric anesthesiology can survive and meet the challenge.

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PEEP AND INTRACRANIAL PRESSURE

Positive end-expiratory pressure (PEEP) was required in 12 head-injured patients in whom intracranial pressure (ICP) monitoring had been previously established. In six, ICP increased by 10 mm Hg or more as 4 to 8 cm H_2O of PEEP were administered. In 10 patients the mean arterial pressure decreased during PEEP. Before PEEP, the mean cerebral perfusion pressure (CPP = BP − ICP) was above 50 mm Hg in all patients. The CPP was less than 50 mm Hg in 6 patients given PEEP. Neurological deterioration occurred in 2 patients during PEEP therapy. In head-injured patients, optimal titration of PEEP therapy should include ICP measurement and/or continuous evaluation of neurologic status. *(Shapiro HM, Marshall LF: Intracranial pressure responses to PEEP in head-injured patients. J Trauma 18:254-256, 1978)*

Automated Measurement and Frequency Analysis of the Pneumocardiogram

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The flow pneumocardiogram (PnCG), ie, measurement of cardiogenic gas movement in and out of the lung during apnea, was transduced by an in-line, high-gain pneumotachograph. A portion of the differentiated PnCG, the dPn/dt IJ wave, has been shown previously to correlate closely with left ventricular function. A simple analog device was designed and tested to measure the dPn/dt IJ amplitude on a practical beat-to-beat basis. Frequency-power spectral analysis showed the PnCG to be a low frequency phenomenon with the systolic component in the 9-to-10-Hz range. Appropriate band-pass filtering of the PnCG and its applicability as an intraoperative monitoring device are presented.

Key Words—MEASUREMENT TECHNICS, pneumocardiography. HEART, pneumocardiography.

THE term pneumocardiogram, based on volume displacement of lung gas, was introduced by Dahlstrom, Murphy and Roos[1] to describe the cardiogenic oscillations observed in single-breath N_2 washout curves. Anesthesiologists routinely observe this phenomenon as the rhythmic pulsations of the reservoir bag in apneic, intubated patients. In 1970 Smith and Reitan[2] identified the pneumocardiogram as a potential monitoring tool for the operating room. They showed that an excellent correlation existed between the IJ wave of the time-differentiated pneumocardiogram (acceleration PnCG or dPn/dt) and maximum ascending aortic blood acceleration and predicted the acceleration PnCG could be utilized for monitoring left ventricular function in patients undergoing anesthesia. Its advantages as an operating room monitor are that the wave form is generally reproducible and that it produces data of physiological significance since the acceleration PnCG varies with changes in heart function.

While it is easy to record, the rapidly moving writeout of the pneumocardiogram is distracting and confusing to most novice observers. This aspect would tend to discourage its acceptance by practicing clinicians. Consequently, an automated system to "read" the pneumocardiogram is needed before it can become a useful tool in patient care and, in fabricating such a device, information about the frequency characteristics of the wave form must be known so that proper active filter design is possible.

The purpose of this paper is to reacquaint readers with the flow pneumocardiogram and its transduction, to investigate its frequency spectrum, and to propose a relatively simple device for automatically processing the wave form.

METHODS

The flow pneumocardiogram (PnCG) is obtained from a small pneumotachograph placed in line between the anesthesia machine and the patient (fig 1). A differential-pressure transducer measures the flow of gas through the pneumotachograph. From a patient intubated or with well-fitted anesthesia mask, the small rhythmic pulsations of gas in and out of the lung are sensed during

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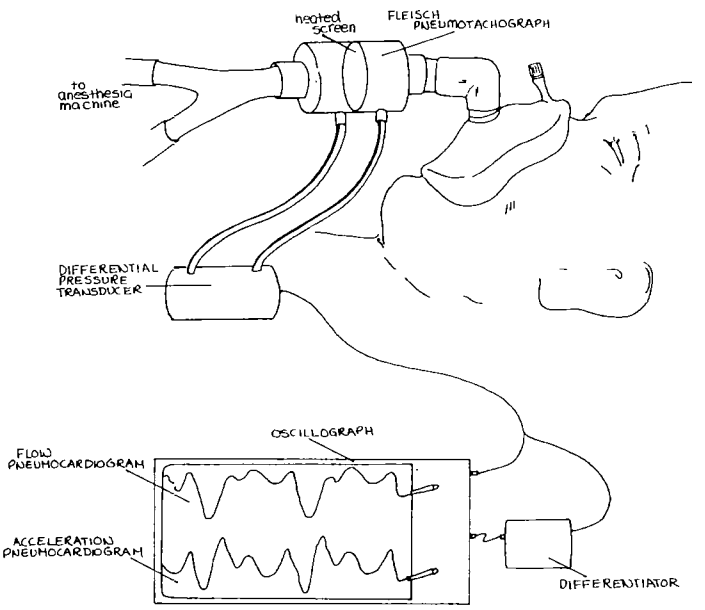


FIG 1. A drawing of the typical arrangement of apparatus for obtaining the PnCG. See text for details.

apnea with the transducer at high gain. Both the flow PnCG seen in the top trace of the oscillograph and its time derivative or acceleration PnCG (dPn/dt) seen on the bottom line can be measured.

Frequency-spectrum analysis of the human PnCG was performed on a PDP-12 computer to assist in optimum design characteristics for filtering the raw wave form. Sixty seconds of unfiltered PnCG obtained at rest from one of the investigators (JAR) through an open glottis at functional residual capacity was placed on FM tape for storage. Separate 2-second frames were independently digitized at 0.5 kHz and their power-frequency spectra measured by a standard subroutine. The average spectrum for 10 frames was plotted for the PnCG example. The same type of PnCG was used for empirical inspection of the HIJ wave frequency by recording the PnCG at 200 mm/sec and measuring the period for the systolic section of the variable, which was assumed to be sinusoidal in nature.

By observing the reproducible wave form of the pneumocardiogram, it was apparent that a simple analog device could measure the IJ wave of dPn/dt on a beat-to-beat basis (fig 2). The concept involves triggering detection of the IJ wave from the ECG or from the dPn/dt wave form itself if the ECG is not available or is distorted by surgical electrocautery. The PnCG signal is filtered at a band-pass frequency of 0.2 to 40 Hz (number 1 on the block diagram) and the acceleration PnCG (dPn/dt) is obtained by active time differentiation (2). A variable one shot (3) masks early unwanted negative waves and the negative peak detector measures the value from zero through the I wave (4). An accessory amplifier converts the voltage to positive ($|\overline{OI}|$) and feeds it to the summing amplifier. When the negative peak is attained, a peak trigger (5) starts positive peak detection to ascertain zero through J (6). When the positive peak is reached, another peak trigger (7) fires a one-shot that signals the sample-and-hold device to sample the output from the summing amplifier. Thus, the absolute sum of the negative and positive peaks—that is, the IJ wave—is measured. A one-shot (8) resets the peak detectors to begin a new search on the next cardiac cycle.

The canine PnCG used in testing the analog circuit was recorded by a Fleisch #1 pneumotachograph with appropriate amplifiers and transferred to FM tape; analog processing was performed on a general purpose analog computer (Beckman 2000 series). The human PnCG's in this paper were transduced by a Fleisch #1 device as well and differentiated on-line. Band-pass filtering at 12dB/octave from 0.2 to 40 Hz was used in recordings for fig 3, 5, and 6. Calibration of the pneumotachograph was performed with gas flow from a standard anes-

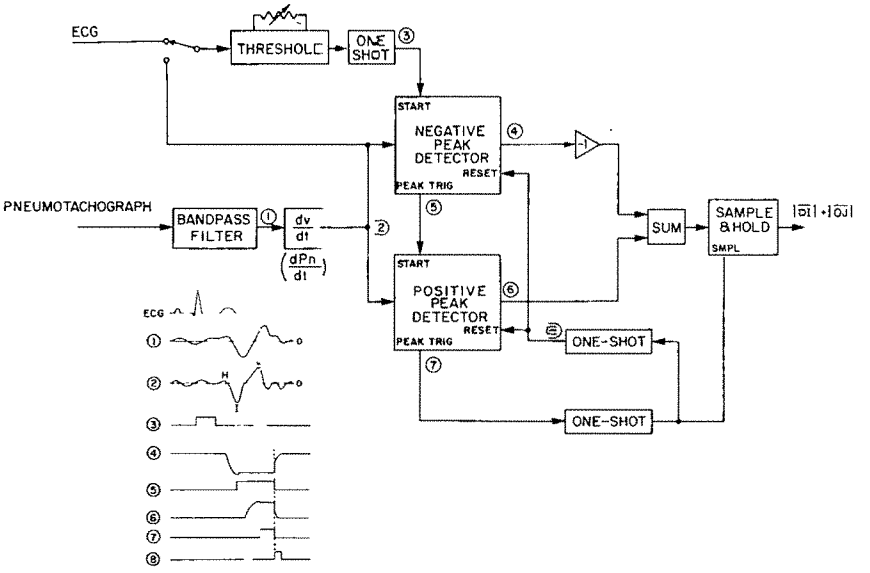


FIG 2. Block diagram for analog detection of dPn/dt IJ wave and line drawing of the sequence. An ECG, filtered PnCG (1) and its time-derivative or acceleration PnCG (2) are the signals processed. The pneumotachograph actually measures velocity, and its derivative should take the form dV/dt. However, a uniform cross-sectional area in the system is assumed in our analysis so that basic units for the PnCG denote flow. A detailed description of the diagram is presented in the text. Numbers at the output of various components correspond to numbers on the appropriate line-drawing voltage curves.

thetic machine. The differentiator was an active system with a 90% rise time of 0.85 msec and was calibrated by voltage from a triangle wave generator.

RESULTS

The top trace in fig 3 shows the PnCG of a subject (JAR) at rest and the differentiated wave form (dPn/dt) on the second line. The repetitive systolic components of the variable, the HIJ wave, are obvious in both recordings. The IJ wave of dPn/dt has a mean control value of approximately 2.5 L/sec^2. Lines 3 and 4 were taken after 2 minutes of running in place, and the average dPn/dt IJ wave value rose to 3.6 L/sec^2. Concomitantly, heart rate increased from 62 to 101 beats/min.

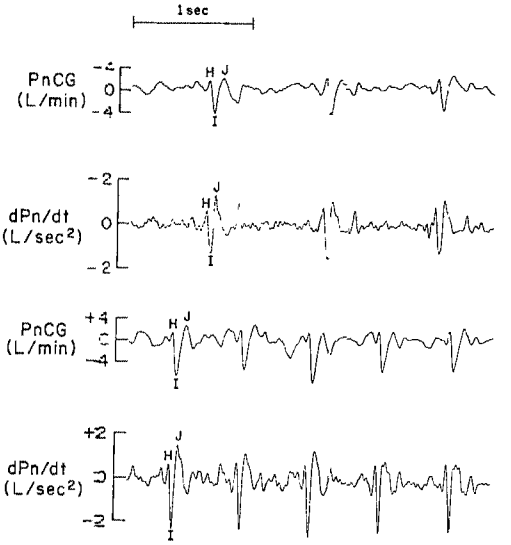


FIG 3. The human PnCG and acceleration PnCG (dPn/dt) during resting control (top two traces) and after exercise (bottom two traces) are shown with units in litres per minute and litres per second per second respectively. The repetitive systolic component in both measurements is identified as the HIJ wave. Flow into the lung is positive (above zero) and flow out of the lung is negative.

The frequency-power spectra analysis for a human PnCG is summarized graphically in fig 4. A large percentage of the power output is at 2 Hz, with similar distinct peaks at 4, 5, and 6 Hz. A secondary rise in energy occurs at 9 Hz with gentle rolloff to 16 Hz. No retrievable energy was found above 16 Hz. Visual inspection of the PnCG recorded at 200 mm/sec showed maximum frequency occurred most often at the positive H or negative I wave peak and was in the 9-to-10-Hz range, which correlates with the small increase in energy at that frequency in fig 4.

Practical testing of the analog technic for measuring the dPn/dt IJ wave is illustrated

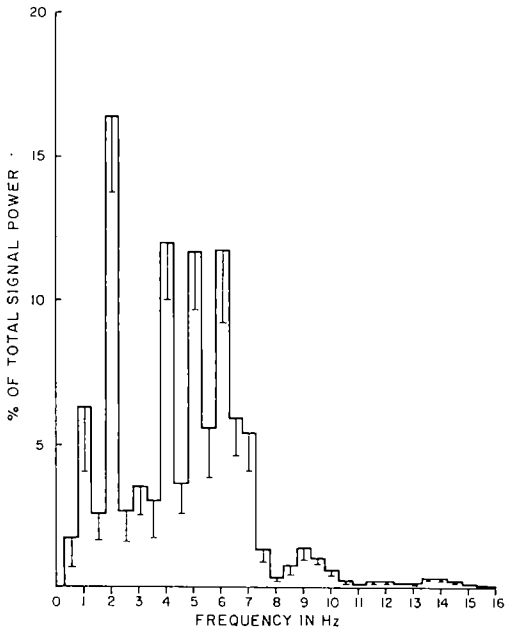


FIG 4. A power-frequency analysis of 10 two-second frames of an unfiltered human PnCG is plotted as the mean value (−1 SEM) at 0.5-Hz intervals. The analog PnCG signal was digitized at 0.5 kHz and analyzed from 0.5 Hz to 20 Hz. There was no observable energy present above 16 Hz. Power at each step is the percentage of total spectral energy at that frequency. Power originally was defined in volts^2.

in a stepwise manner (fig 5). A threshold was detected from the ECG, and the sequence of peak detection and output summing was similar to the protocol outlined in fig 2. In this case, the canine heart was markedly depressed by 2% inspired halothane anesthesia, and the average dPn/dt IJ wave acceleration was 760 ml/sec^2. Small beat-to-beat variations in the sample-and-hold values can be seen in the bottom trace.

The effect of varying concentrations of halothane on another animal's pneumocardiogram showed a stepwise reduction in the automatically computed dPn/dt IJ wave as end-tidal gas concentrations increased (fig 6). Interestingly, most of the total IJ amplitude change resulted from attenuation of the negative wave ($|\overline{OI}|$). In this example the decrease in cardiac inotropy expressed by the dPn/dt IJ wave was from 2500 ml/sec^2 to 500 ml/sec^2, or a fall of 80% as halothane concentration quadrupled.

DISCUSSION

Acceptance of a new noninvasive monitoring technic depends primarily on the fulfillment of 2 criteria: first, the method must easily obtain practical information not readily available from current measurements, and, secondly, it must present the data in a simple fashion clearly understood by practicing clinicians.

The work by Smith and Reitan[2] showed the first criterion was met by the acceleration PnCG, since the dPn/dt IJ wave was closely correlated to ascending aortic blood acceleration as an index of myocardial contractility. In order to satisfy the second criterion, our present study has demonstrated the feasibility of measuring the dPn/dt wave automatically on a beat-to-beat basis with an output voltage calibrated to give clear functional information to the observer. For example, the stepwise reduction in the computed dPn/dt IJ amplitude corresponding to increasing halothane concentration (fig 6) can give immediate feedback to the clinician concerning heart function during cardiac depression from a potent anesthetic agent.

The pneumocardiogram as a monitoring tool has the advantages of simple transduction and little interference with surgical procedures or patient comfort. In obtaining the record for fig 3, the pneumotachograph was connected in a fashion similar to the arrangement in fig 1 and the glottis of the subject remained open during a respiratory pause. There was virtually no discomfort involved, and the transducer and anesthesia mask were hand held by the subject during a resting period. However, the differential-pressure transducer, pneumotachograph, and connecting lines are all susceptible to considerable motion artifact so that in clinical situations the transducer should be cushioned in foam rubber and the pneumotachograph apparatus suspended from elastic supports.

Common heart-monitoring indices involve either cardiac-event timings (eg, systolic time intervals) or measurements of changes in chamber or peripheral pressures (eg, left ventricular dP/dt and tension-time index). There is reasonably direct coupling between the heart and the index measured in these cases. However, with the PnCG, blood ejecting into the ascending aorta expands the mediastinum and compresses contiguous lung tissue with each pulse to displace the gas generating the PnCG.[4] This compressible gas volume (the volume of functional residual capacity) effectively damps some of the higher frequency cardiac signals. In

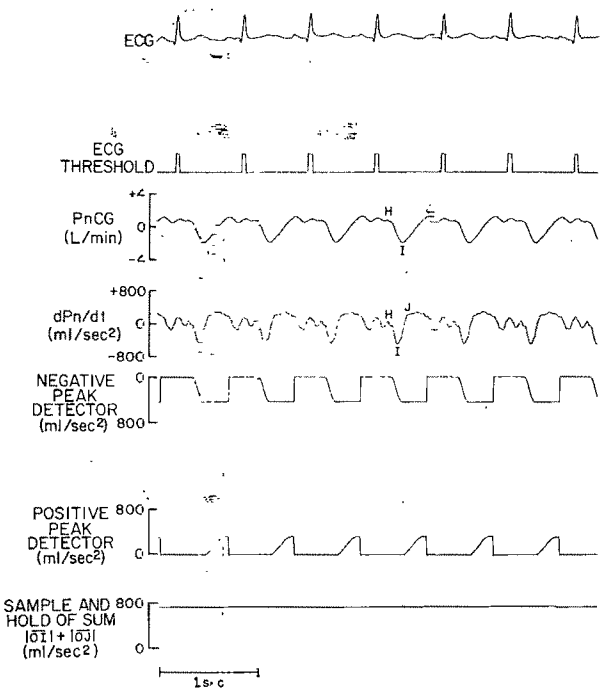


FIG 5. The working principle of analog measurement of a dPn/dt IJ wave involves a comparator to detect onset of QRS in the ECG, thereby activating a negative peak detector on the dPn/dt I wave after a short delay to eliminate tracking earlier negative waves. The positive peak detector is started once the negative peak is reached. A summing amplifier output in the last line gives beat-to-beat amplitudes of the dPn/dt IJ wave in units of millilitres per second per second. $|\bar{OI}| + |\bar{OJ}|$ are the sum of absolute values for amplitudes from zero to the I-wave peak and zero to the J-wave peak.

addition, the pneumotachograph is usually connected to the subject by a compliant rubber face mask or endotracheal tube, which could lead to further diminution of high-frequency components in the PnCG. Not surprisingly then, the frequency-power spectrum showed that a large proportion of PnCG energy occurs below 7 Hz (fig 4). On the other hand, the PnCG analyzed was obtained at rest; with increased heart rate and contractility, as seen in the bottom traces of fig 3, the H and I peaks became sharper, indicating a higher frequency spectrum by visual inspection at least. Most probably the PnCG frequency response is both rate and inotropy dependent.

From the frequency-power curve, filter characteristics for processing the PnCG were selected. A high-pass filter at 0.2 Hz was used to eliminate ultralow-frequency baseline wander, and the low-pass frequency of 40 Hz was chosen since it was approximately 4 times the fundamental frequency of the HIJ wave. In this way, first and some second harmonics of the wave should be preserved, but unwanted high-frequency noise will be eliminated. In our experience, the 40-Hz value is equally effective and valid with increased heart rate and inotropy. For example, in fig 3 the dPn/dt IJ wave increased 44% with exercise above the resting value. Peak edges remained sharp, with no visual indication of slurring or distortion by the band-pass filtering of the PnCG at increased contractility levels. On a physiological basis, this human example supports more elaborate animal studies on the relationship of the pneumocardiogram to cardiac inotropy.[2,3] While recent work has shown that the dPn/dt IJ wave is both afterload and preload dependent in dogs,[4] it is not affected substantially more by loading changes than other commonly used monitoring variables.[5-8]

In summary, this investigation has shown the feasibility for on-line beat-to-beat measurement of the dPn/dt IJ wave as a cardiac-function monitor. With a relatively low fundamental frequency, the PnCG is easily transduced and processed. Hopefully, further investigation into the clinical application of the pneumocardiogram will be made, and operating room use of this unique monitoring technic will be forthcoming.

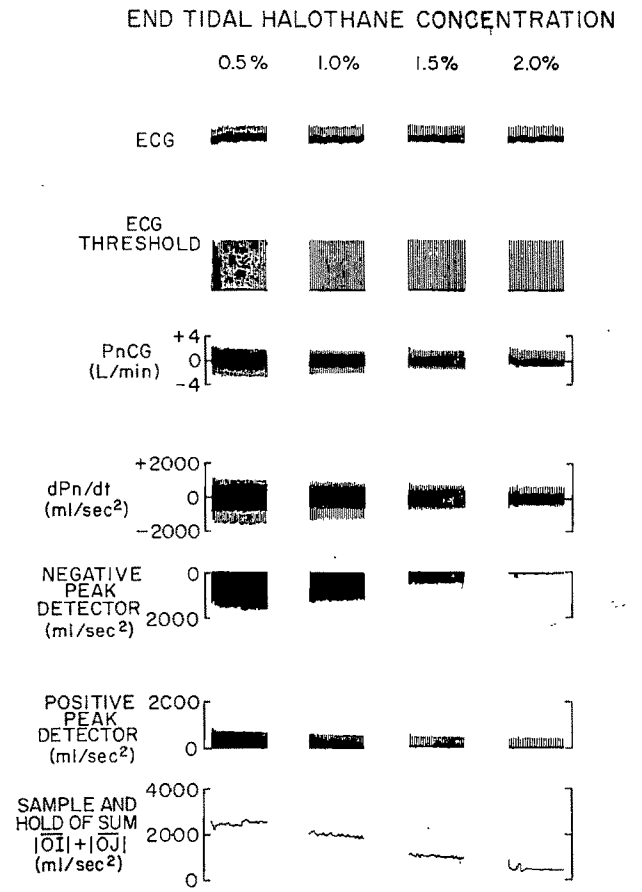


FIG 6. The effect of a stepwise increase in halothane concentration on the dPn/dt IJ wave is computed in a fashion similar to that in fig 5. The flow and acceleration (dPn/dt) pneumocardiograms are shown with the dPn/dt negative and positive peak detectors triggered from the ECG threshold. The bottom line demonstrates the beat-to-beat decrease in the dPn/dt IJ wave amplitude as halothane concentration increases.

ACKNOWLEDGMENT

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Determinants and Genesis of Canine Pneumocardiogram

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The pneumocardiogram measures the to-and-fro movement of gas from the lung with each heartbeat during apnea. Six mongrel dogs were prepared with chronic ascending aortic or pulmonary artery flow probes, corresponding occlusion cuffs and intraventricular pressure transducers. Under halothane anesthesia, the flow pneumocardiogram (PnCG) and its time derivative (acceleration pneumocardiogram or dPn/dt) were transduced during apnea by a small high-gain pneumotachograph. All variables were recorded on paper. The effects on the pneumocardiogram of great vessel occlusion, changes in cardiac loading, small airway patency, and chest wall integrity were investigated. Four of the animals were treated subsequently to produce a chemical cardiac denervation and restudied. The systolic component of the dPn/dt which correlates with myocardial contractility (IJ wave) was dependent primarily on left ventricular (LV) ejection, markedly affected by cardiac preload and modified by afterload changes to a lesser degree. Small airway closure obliterated the wave form, while opening the chest wall attenuated the dPn/dt IJ wave by 25%. This study shows the dPn/dt IJ wave is anatomically related to LV performance and responds to changes in LV function similar to other noninvasive cardiac measurements.

Key Words—MEASUREMENT TECHNICS, pneumocardiography. HEART, pneumocardiography. LUNG, pneumocardiography.

For years anesthesiologists have observed movement of the anesthetic reservoir bag synchronus with the heartbeat during apnea in anesthetized patients. This movement, caused by gas flowing into and out of the lungs with each cardiac cycle, has been the subject of scientific curiosity for several decades.

The term pneumocardiogram was introduced by Blair and Wedd[1] to describe the phasic changes in thoracic volume during the cardiac cycle. They used airway pressure measurements and assumed constant chest compliance to calculate volume variations. Luisada[2] reviewed the literature on the pneumocardiogram in 1942 and again measured the upper airway pressure waves caused by the beating heart in a series of patients. Dahlstrom, Murphy, and Rocs[3] reinstituted the term pneumocardiogram to describe the rhythmic cardiogenic gas-flow oscillations in single-breath N_2 washout curves. In 1960 both Langer, Bornstein, and Fishman[4] and Hugh-Jones and West[5] suggested that this pulsatile mixing of lung gases was caused by the heart and great vessels alternately compressing and expanding the perihilar pulmonary tissue, while Josenhans[6,7] postulated the "air pulse" (pneumocardiogram) was derived from intrathoracic blood volume variation over the cardiac cycle. Subsequently, Verdouw,[8] in a theoretical analysis of blood flow within the great vessels of the chest, produced wave forms remarkably similar to the experimental pneumocardiogram. Interest in the wave forms remained mostly academic until 1970 when Smith and Reitan[9] published a report on the potential use of the pneumocardio-

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gram as a clinical tool for monitoring heart function because of the close correlation of acceleration of gas out of the lung to cardiac inotropy. The purpose of this study is to investigate the hemodynamic factors affecting the pneumocardiogram and to gain insight into the genesis of the acceleration wave form.

METHODS

Surgical Preparation—Six mongrel dogs (average weight = 22.3 ± 1.2 kg) were prepared through a left lateral thoracotomy in the following manner: 2 dogs had placement of ascending aortic flow probes and pulmonary artery occlusion cuffs; 2 dogs were fitted with pulmonary artery flow probes and ascending aortic occlusion cuffs; and 2 dogs had inferior and superior vena cavae flow probes and pulmonary artery occlusion cuffs placed. The flow probes were pulsed ultrasonic devices, excited and triggered by a Beckman experimental unit. Response linearity to 40 Hz was presumed from design specifications. The occlusion cuffs were silastic balloons with provisions for external inflation. Each cuff was calibrated before installation for the volume sufficient for total closure. Postmortem examination revealed near complete occlusion of the vessel when the prescribed amount of H_2O filled the cuff.

Besides the flow probes and occlusion cuffs, each animal was implanted with miniature pressure transducers (Konigsberg P-20) in the left and right ventricle and left subclavian artery and polyethylene catheters into the left carotid and external jugular vein advanced into the ascending aorta and right atrium respectively. All catheters, transducer connections, and occlusion-cuff tubing were exteriorized on the dorsum of the animal's neck and placed in a protective canvas pouch. Following this surgery, the dogs were observed for a period of 12 to 16 days until recovery was complete, measured by normal activity, temperature, and blood count values. The atrial and aortic lines were kept patent by periodic flushing with a dilute heparin solution.

Experimental Preparation—At the time of study, anesthesia was induced with thiopental (15 mg/kg), and endotracheal intubation was performed. Anesthesia was maintained with 1% inspired halothane in O_2 and pancuronium (0.1 mg/kg). Ventilation was controlled with a Harvard piston apparatus at a volume to keep the $Paco_2$ at about

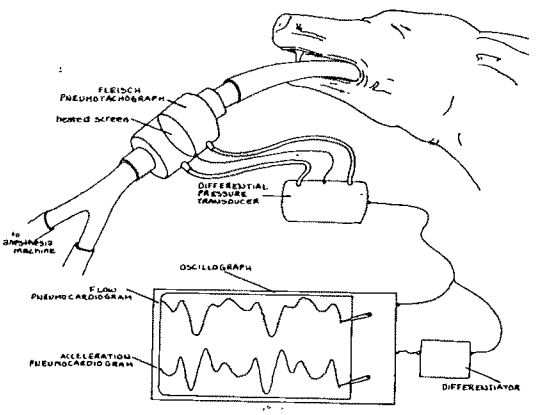


FIG 1. The apparati for measuring the flow (velocity) and acceleration PnCG are shown. The pneumotachograph is turned to high sensitivity, and during the apnea the wave forms are recorded on the oscillograph. Flow calibration is done with known gas-flow rates from an anesthetic machine, and the differentiator is calibrated electronically with a triangle-wave-form generator.

30 torr. A #1 Fleish heated pneumotachograph was placed between the endotracheal tube and the anesthetic hose Y-piece (fig 1). At high sensitivity during apnea, the pneumocardiogram was transduced by this device. A standard lead II ECG was monitored and a peripheral venous line placed. Through the right external jugular vein a #5F Swan-Ganz catheter was floated into the pulmonary artery. From the implanted and attached sensors the following variables were recorded onto an oscillograph and transferred to FM tape:

(1) Left ventricular pressure (LVP), maximum positive time derivative of LVP (LV dp/dt), and left ventricular end-diastolic pressure (LVEDP).

(2) Phasic pulmonary artery and ascending aortic pressure, electronic mean ascending aortic pressure (AP), and central venous pressure (CVP).

(3) Phasic flow signals from the vena cavae, pulmonary artery, and ascending aorta (Q); differentiated aortic flow (ascending aortic blood acceleration—dQ/dt).

(4) The velocity pneumocardiogram (PnCG) and its time derivative, the acceleration PnCG (dPn/dt).

(5) R-R interval from the ECG.

The animals received maintenance 0.45% NaCl and 5% dextrose IV at 4 ml/kg/hr and temperature was held at 37 C with heating pads and lamps. The miniature pressure transducers were calibrated at 37 C

prior to implantation and adjusted appropriately, if necessary, at the time of the experiment by comparison with values from the indwelling catheters connected to Statham model P-23Db pressure modules. The differentiators were active devices with 90% rise time of 1.8 msec. The PnCG was conditioned with an active, linear phase shift, low-pass filter prior to differentiation. Time lag of the PnCG from the filter was about 2 msec at the common PnCG frequency (10 Hz).

Protocol — After anesthetic stabilization, several interventions were performed while recording all variables. First, the ascending aortic and pulmonary artery occlusion cuffs were inflated in appropriate dogs. The completeness of occlusion was determined by sudden pulmonary artery pressure drop with vena cavae flow cessation during pulmonary artery occlusion and $\overline{AP}$ fall with LVP rise during ascending aortic occlusion. Secondly, to produce a sudden decrease in preload, 10% of the calculated blood volume—8 ml/kg—was withdrawn rapidly and subsequently reinfused. Next, after pressure values returned to control levels, an equivalent amount of Ringer's lactate solution was injected peripherally over 30 seconds to acutely increase the cardiac preload. A prolonged equilibration period followed to allow the recorded variables to approach original control levels. Thereafter, cardiac afterload ($\overline{AP}$) was lowered 30% by a constant venous infusion of sodium nitroprusside. Upon recovery a slow venous infusion of phenylephrine raised afterload by 30 to 40%. In some dogs the final chemical intervention entailed injection of nebulized ammonia solution down the endotracheal tube and subsequent administration of small IV increments of isoproterenol until the PnCG reappeared.

At a later time 4 dogs were restudied after chemical denervation of the heart was obtained by treatment with 10 mg/kg of practolol (a predominantly β_1 blocker) and 0.5 mg/kg of atropine IV. Denervation was produced to eliminate reflex adjustment of heart function to loading changes and was considered complete if no pulse-rate change occurred following the infusion of 2 μg of isoproterenol. The same experimental protocol was followed in the "denervated" animals as in the innervated dogs: occlusions followed by preload and afterload alterations.

Among 4 dogs the effects of chest wall

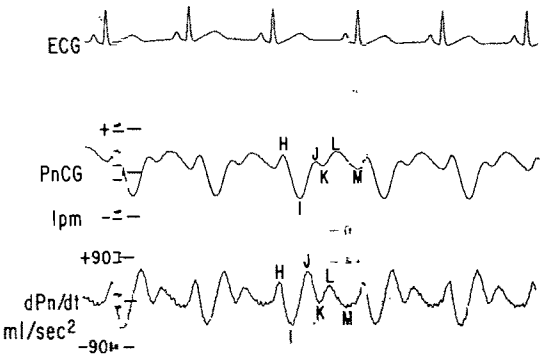


FIG 2. Typical ECG, velocity pneumocardiogram (PnCG), and acceleration pneumocardiogram (dPn/dt) from a dog are shown. Units are in litres per minute (lpm) and millilitres per second per second (ml/sec²) for the PnCG and dPn/dt respectively. Both share common nomenclature; systolic wave forms are HIJ, and diastolic are KLM. On the PnCG, flow into the lung is positive (above 0) and flow out of the lung is negative (below 0). The dPn/dt is the time derivative of PnCG and follows the slope of the PnCG in an analog fashion.

integrity upon the pneumocardiogram was observed as first one side of the thorax and then the other was opened in randomized sequence. Finally the dogs were sacrificed to retrieve the hardware. Placement of all sensors was checked at postmortem examination.

At steady state runs during preload and afterload alterations and with chest opening, the primary measurements and derived variables were taken from the mean values of 10 consecutive heartbeats. With dynamic interventions such as great vessel occlusion, the average of 5 consecutive heartbeats at maximum change was taken as the reported value. All readings were done at a paper speed of 50 mm/sec during apnea produced by disconnecting the ventilator. The data were analyzed on a Tektronix Model 31 Programmable Calculator, and statistical significance determined by a standard Student's *t*-test.

RESULTS

Figure 2 illustrates a typical pneumocardiogram with the HIJ wave labeled on both the velocity (PnCG) and acceleration (dPn/dt) measurements. The IJ wave of the acceleration PnCG was the segment investigated most thoroughly in this study since it is the wave that correlates well with the cardiac inotropic state.[9]

The effect of acute pulmonary artery occlusion is shown in fig 3. Left ventricular

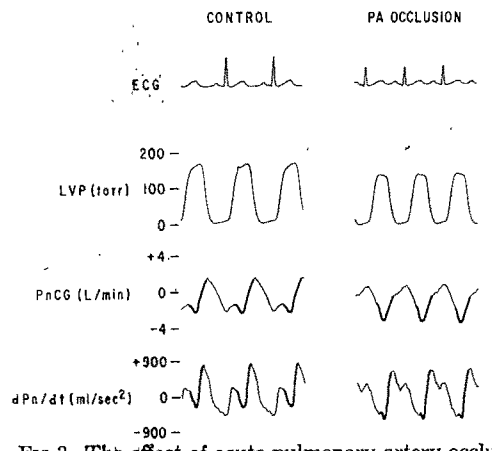


FIG 3. The effect of acute pulmonary artery occlusion on the ECG, left ventricular pressure(LVP), PnCG, and dPn/dt is shown. The HIJ wave on both the PnCG and dPn/dt is hand darkened for easier visualization. Control values are in the normal range and upon occlusion, LVP, PnCG IJ, and dPn/dt HI wave decreased while heart rate and PnCG HI increased slightly. dPn/dt IJ wave was relatively unchanged.

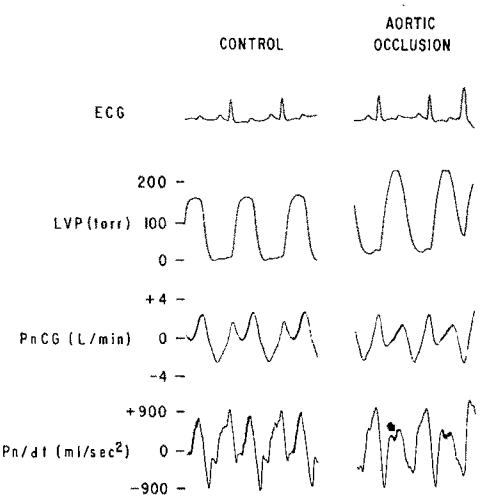


FIG 4. The effect of acute ascending aortic occlusion on ECG, LVP, PnCG, and dPn/dt is shown. Again, the HIJ waves in the velocity and acceleration PnCG's are outlined. The left panel displays control values, and measurements on the right were taken after aortic occlusion. The acute left heart strain from the outflow obstruction produced a premature ventricular contraction seen as the last beat of the second sequence.

peak and end-diastolic pressure decreased while the PnCG HI wave increased and the IJ wave decreased. The dPn/dt IJ wave remained relatively unchanged but its HI wave abruptly decreased. This effect was reproducible in all dogs undergoing pulmonary artery occlusion.

On the other hand, acute aortic occlusion resulted in near obliteration of the acceleration PnCG IJ wave (fig 4). In the control series dPn/dt has a value of about 875 ml/sec²; upon occlusion the IJ value is reduced to about 125 ml/sec² (see arrow). Concurrently LVP rose and LVEDP increased greatly. The PnCG HI wave was markedly attenuated. Apparently the acceleration IJ wave is primarily dependent upon left ventricular ejection.

A graphic summary of our findings on factors modifying the IJ wave of the velocity (PnCG) and acceleration (dPn/dt) pneumocardiograms is shown in fig 5. Both innervated (I) and chemically denervated (D) dogs are included in most of the interventions. With aortic occlusion (AO) the dPn/dt IJ wave was reduced to a mean value of 25% of control. The PnCG demonstrated a trend toward attenuation that was not statistically significant. Pulmonary artery occlusion (PO) significantly attenuated the PnCG to 50% of control in both innervated and denervated animals while the acceleration IJ wave remained at 90% or above. With volume loading the intact dogs showed insignificant IJ wave changes but in the denervated preparation a significant increase was evident. However, reduction of circulating volume resulted in a marked decrease in the IJ wave in all animals. Only 2 dogs were studied for volume reduction in a denervated state so that statistical significance could not be determined in these. Increasing the afterload produced a statistically insignificant increase in dPn/dt IJ wave amplitude. Reduction of afterload significantly decreased the dPn/dt IJ wave in innervated dogs but had no effect in the denervated ones.

A compilation of the protocol effects in innervated animals is listed in table 1. In most cases the dPn/dt IJ wave varied in a similar fashion to dQ/dt and LV dP/dt, but was depressed to a far greater degree with volume reduction. Interestingly, dQ/dt increased erratically in response to a decrease in afterload while both LV dP/dt and the dPn/dt IJ wave were depressed significantly. With changes in pre- and afterload the R-R interval responded appropriately.

In the chemically denervated dogs undergoing the same protocol, R-R interval changes were generally reversed (table 2). Decreasing preload or afterload increased the R-R interval and increasing the AP

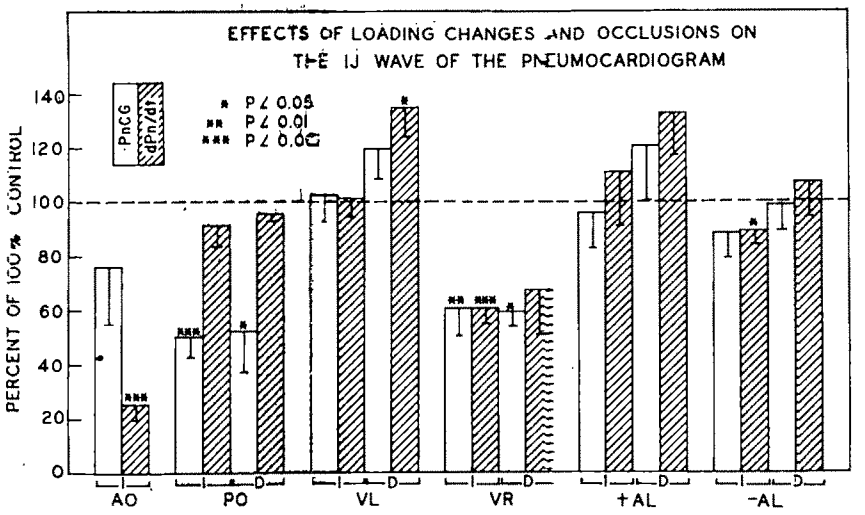


FIG 5. The effects of several physical and chemical hemodynamic interventions upon the PnCG and dPn/dt IJ waves are described by bar graph measured as a percent of each 100% preintervention control. The responses to acute aortic occlusion (AO), acute pulmonary artery occlusion (PO), a sudden 10% increase in circulatory volume load (VL), a comparable 10% volume reduction (VR), a 30% increase in $\overline{AP}$ or afterload (+AL) and a 30% decrease in afterload (−AL) are displayed with their corresponding standard errors of the mean. The asterisks denote varying statistical significance. The clear bars show the response of the IJ wave of the velocity PnCG while the hatched ones designate changes in the acceleration-PnCG IJ wave. The letter I stands for innervated dogs and D for chemically denervated animals.

TABLE 1
Innervated Dogs

	R-R	$\overline{AP}$	dQ/dt	LV dP/dt	PnCG	dPn/dt
Aortic occlusion	98.7	55.3†	...	97.2	76.9	25.7‡
	±1.0	±10.4	...	±4.4	±21.3	±6.0
	(6)	(5)	...	(6)	(6)	(6)
Pulmonary artery occlusion	99.8	91.9*	96.0†	89.6	50.2‡	91.4
	±1.6	±3.6	±1.1	±5.4	±7.4	±8.0
	(7)	(7)	(5)	(7)	(7)	(7)
10% volume load	102.1	102.0	100.3	104.0	102.6	101.2
	±1.7	±2.5	±4.6	±4.5	±9.6	±6.9
	(6)	(6)	(3)	(6)	(6)	(6)
10% volume reduction	96.0	92.4*	90.2	92.8	60.1†	60.8‡
	±2.0	±2.1	±2.8	±3.8	±9.5	±6.0
	(4)	(4)	(2)	(4)	(4)	(4)
Afterload increase	108.3†	144.6*	102.2	115.2	95.7	111.4
	±1.8	±17.0	±6.5	±8.1	±12.4	±19.9
	(6)	(6)	(3)	(6)	(6)	(6)
Afterload decrease	94.4	65.1‡	122.2	90.9*	88.4	89.1*
	±5.4	±3.1	±20.7	±4.0	±9.1	±4.7
	(6)	(6)	(4)	(6)	(6)	(6)

Effects of various interventions in innervated dogs on the R-R interval, mean arterial pressure ($\overline{AP}$), maximum ascending aortic blood flow acceleration (dQ/dt), maximum positive time derivative of left ventricular pressure (LV dP/dt), IJ wave of the velocity pneumocardiogram (PnCG), and the IJ wave of the acceleration pneumocardiogram (dPn/dt). All results are expressed as a percent of the preintervention control ± 1 SEM. The numbers in parentheses denote the number of runs at each sample point. On occasion, a duplicate intervention was performed during pulmonary artery and aortic occlusion when such manipulation was easily repeatable. Statistical significance is shown by reference signs: $p<0.05$ (*), $p<0.01$ (†), and $p<0.001$ (‡).

TABLE 2
Chemically Denervated Dogs

	R-R	$\overline{AP}$	dQ/dt	LV dP/dt	PnCG	dPn/dt
Pulmonary artery occlusion	99.7 ±0.4 (3)	79.3† ±4.9 (3)	93.7† ±0.5 (2)	97.4 ±4.8 (3)	52.1* ±14.9 (3)	95.6 ±2.7 (3)
10% volume load	105.4 ±3.9 (4)	103.8 ±3.1 (4)	108.3 ±2.9 (2)	109.4* ±3.0 (4)	119.8 ±11.6 (4)	134.4* ±10.3 (4)
10% volume reduction	102.6* ±0.5 (2)	92.3 ±2.5 (2)	87.2 ... (1)	91.3 ±3.0 (2)	59.1* ±5.6 (2)	67.6 ±16.8 (2)
Afterload increase	98.1 ±0.8 (5)	130.7‡ ±4.6 (5)	78.3 ±8.0 (2)	115.9* ±6.4 (5)	120.3 ±20.0 (5)	132.8 ±16.5 (5)
Afterload decrease	102.6 ±4.6 (4)	71.1‡ ±2.2 (4)	112.2 ... (1)	82.5* ±5.4 (4)	98.3 ±9.2 (4)	107.0 ±12.4 (4)

The effects of similar interventions mentioned in Table 1 on the same cardiovascular variables are listed for chemically cardiac-denervated dogs. There were no animals undergoing aortic occlusion in this series. Data presentation and denotation of statistical significance are the same as in Table 1.

shortened it slightly. Changes in dQ/dt, LV dP/dt, and the IJ waves were usually similar to the changes in the intact animals except that in the denervated dogs, volume loading and decreased afterload augmented the dPn/dt IJ wave. Variation of the indices of heart function were similar in both groups of animals except that denervation unveiled depression of dQ/dt with increased afterload.

Obviously, the pneumocardiogram is dependent on a patent airway system. Figure 6 shows the effect of inhaled ammonia and

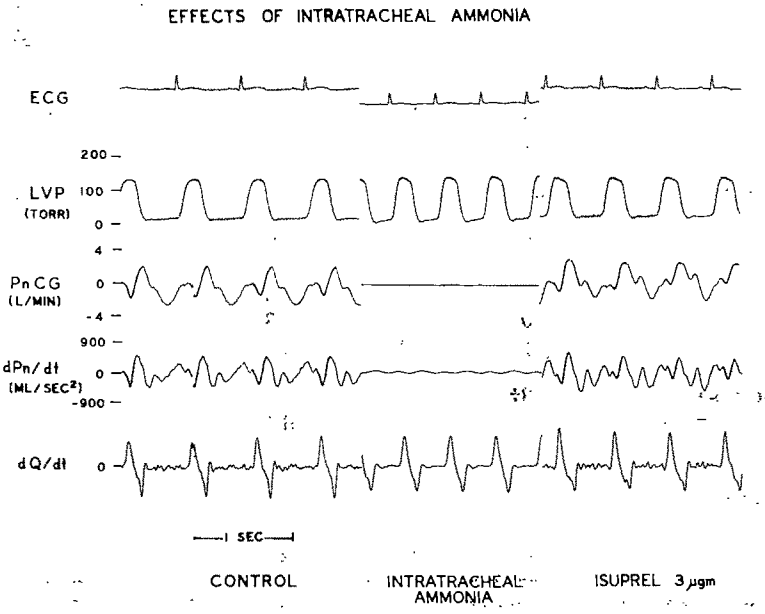


FIG 6. The ECG, left ventricular pressure (LVP), velocity pneumocardiogram (PnCG), acceleration pneumocardiogram (dPn/dt), and ascending aortic blood acceleration (dQ/dt) are shown before, during, and after the installation of nebulized ammonia into an animal's airway. The units for each variable are similar to fig 3, and dQ/dt measures only relative change since the aortic flow probe in this dog was not calibrated for specific blood output. The HIJ waves are outlined as before. While ammonia obliterated the PnCG and dPn/dt, the other variables were substantially unchanged. Intravenous isoproterenol (Isuprel®) renovated the wave forms in both pneumocardiogram measurements.

TABLE 3
Effects of Chest Opening

	R-R	$\overline{AP}$	dQ/dt	LV dP/dt	PnCG	dPn/dt
One side	102.3 ±3.2 (4)	90.2 ±8.5 (4)	96.0 ±3.3 (2)	102.0 ±7.8 (4)	66.8† ±6.5 (4)	88.4 ±9.6 (4)
Both sides	101.7 ±3.4 (4)	90.7 ±9.4 (4)	91.3* ±3.6 (2)	93.3 ±5.0 (4)	55.8* ±15.4 (4)	74.2* ±9.5 (4)

The effects of randomly opening both chest cavities on cardiovascular variables are listed for 4 dogs. The actual variables, the denotation of statistical significance, and the meaning of parenthetical numbers are similar to those in tables 1 and 2.

the resultant bronchospasm on the wave forms. There was complete obliteration of pulsatile air flow after the ammonia even though LVP and dQ/dt were substantially unchanged. A small amount of IV isoproterenol reversed the bronchoconstriction and the wave form reappeared.

An intact chest wall was not required for transduction of dPn/dt. Table 3 illustrates the effect of randomly violating the chest wall continuity by large incisions into the pleural space. Arterial pressure, heart rate, and ascending aortic blood acceleration all fell slightly. PnCG fell significantly and progressively as each side was opened. However, dPn/dt diminished considerably less, to 74% of control, with bilateral loss of pleural continuity. Apparently a substantial portion of the acceleration PnCG is not dependent on an intact chest wall.

DISCUSSION

Our investigation has uncovered several interesting factors concerning the pneumocardiogram. The first among these involves the specific pulmonary origin of its wave form.

In describing the mechanism of reflex airway closure by inhaled irritants, Mills et al[10] and Widdicombe[11] reported that treatment with IV isoproterenol effectively blocked the vagally transmitted impulses causing bronchial and bronchiolar constriction. Maximum sympathetic control of canine airway musculature was demonstrated by Carbezas et al[12] to reside in airways from less than 1 through 5 mm in diameter. These include the small segmental bronchi down to the terminal bronchioles.[13] Consequently, the fact that airway obstruction caused by intratracheal ammonia in our dogs was reversed by isoproterenol leads us to believe that the general site of action of ammonia must be muscle groups under β_2 adrenergic control such as the helical bands found in these small bronchi and bronchioles and that the anatomic origin of the PnCG must be distal to the site of constriction—that is, the respiratory bronchioles and alveoli—or in the small bronchi and bronchioles themselves. If this is so, it is reasonable to assume that pulmonary blood volume changes in the capillaries and vessels around the respiratory bronchioles and alveoli may induce the systolic wave form seen on the pneumocardiogram. This arrangement would implicate right ventricular dynamics in the genesis. However, sudden pulmonary artery occlusion attenuated only the HI segment of the dPn/dt and left the IJ wave relatively unchanged (fig 3 and 5). Seemingly, the assumption that right-sided systolic events cause the dPn/dt IJ does not hold true.

Conversely, in occluding left ventricular outflow, the dPn/dt IJ was dramatically reduced (fig 4 and 5). The dPn/dt IJ wave is derived from the PnCG starting near the O point on the PnCG HI wave and continues to about the O point on the PnCG IJ wave (fig 2). This flow segment is entirely negative so that flow is out of the lung. Therefore it appears that the dPn/dt IJ is the result of acceleration of gas out of the lung and is dependent on left heart systole.

There are several possible explanations for this observation. Since air is moving out of the lung, lung volume is being reduced, presumably by pulsatile expansion of contiguous structures. Appropriate timings of PnCG and blood flow are necessary for understanding the flow relationships. From fig 7 it may be seen that the onset of ascending aortic flow precedes the advent of gas flow out of the lung by about 60 msec. Similarly, peak ascending aortic blood-flow acceleration occurs about 60 msec before maximum acceleration of gas out of the lung (the initial steep slope of the dPn/dt IJ wave). Assuming an

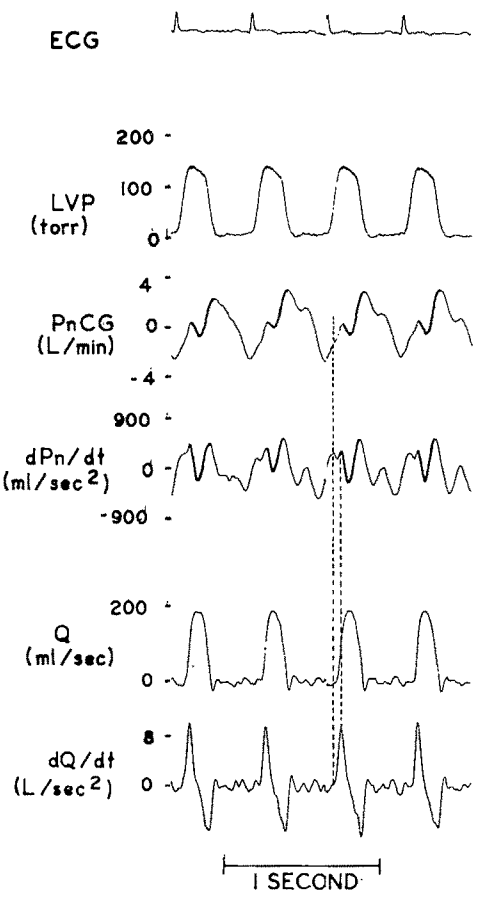


FIG 7. Timing diagram illustrating the relationship between blood flow and acceleration out of the left ventricle, and gas flow and acceleration out of the lung. The ECG, left ventricular pressure (LVP), velocity pneumocardiogram (PnCG), ascending aortic flow (Q), and ascending aortic blood flow acceleration (dQ/dt) with their respective units are shown. The HIJ waves are darkened to enhance identification. The onset of ascending aortic flow—denoted by the first dashed line—precedes the start of gas flow out of the lung measured as the O point on the PnCG HI wave by approximately 60 msec. Similarly, maximum ascending aortic blood flow acceleration—measured from the peak of dQ/dt by the second dashed line—precedes the initial steep slope on the dPn/dt IJ wave (the maximum acceleration of gas out of the lung) by 60 to 65 msec.

average 65-cm distance from the pneumotachograph to the small airways in the canine lung, mean gas-flow wave velocity would be approximately 10.8 m/sec in order to cover that distance in 60 msec. This figure is within reason for laminar flow of low-density gas.

What structures could cause the lung compression? The change in cardiac dimensions during systole is in the wrong direction; that is, total volume decreases and could not account for lung compression. Alternatively, the bolus of blood ejected from the ventricle moves as an expansive, pulsatile mass up the ascending aorta and, through the mediastinal walls, has compressive influence on lung tissue and the potential for gas displacement from the small airways. This explanation is in agreement with the theoretical proposal of Verdouw et al.[8] The duration of the dPn/dt IJ wave (and consequently the outward gas flow on the HI—IJ waves of the PnCG) is about 60 msec. With an 8 m/sec blood pulse wave velocity,[14] this is sufficient time for the pulse to travel about 0.5 m, which would move it out of the thoracic cavity.

Another possibility is that pulsatile blood flow in bronchial arteries was responsible for the lung gas displacement. While these arteries do supply lung nutrition as far as the terminal bronchioles, there are two factors against their being the cause of the gas displacement. First, the arteries come off the thoracic aorta or intercostal branches so that there would be an additional time delay in generating the lung tissue displacement. At least another 50 msec would be necessary for the pulse wave to travel to these small arteries. Such a delay would seem to preclude bronchial arteries as an explanation for this phenomenon. Secondly, about 2 to 4 ml of gas were displaced with each systole. An equal amount of blood must be accounted for. If this were to come from the bronchial arteries, they would account for up to 10% of the stroke output. This is an unrealistic figure and seemingly rules out the proposal.

From table 3 it was seen that the dPn/dt IJ wave was not obliterated by opening the thorax to the atmosphere. In other words, increases in chest wall compliance did not greatly reduce the dPn/dt IJ wave. An explanation of this circumstance may be that with disruption of the intrapleural negative pressure and resulting pulmonary deflation, the lung retracted even closer to the hilum and, consequently, maintained contiguity with the mediastinum and great vessels. This arrangement would allow the pulsatile flow of blood in the aorta to be transmitted to the lung tissue in spite of an open chest wall and would account for the continued movement of gas in and out of the lung with each heartbeat.

While it was not our specific intent to compare the pneumocardiogram comprehen-

sively to other indices of ventricular performance in this study, the changes we observed in dQ/dt and LV dP/dt_{max} during variations in preload and afterload resemble the findings of other authors.[15,16] Although our sample of data points is small for these variables so that absolute significance is often lacking, this confirmation of previous investigations would seem to validate our animals as hemodynamic models. Interestingly, in the chemically denervated animals, changes in heart rate as a consequence of changes in preload and afterload were usually reversed compared to the intact dogs, although none was statistically significant. This paradoxical response is similar to data accumulated in other surgically denervated canine heart models.[17] The small slowing of heart rate following variation in preload and afterload may be the result of some intrinsic mechanism unblocked by our technic or may be accentuated by the direct myocardial depressant effect of the anesthesia.[18]

In conclusion, this study defines the hemodynamic factors influencing the IJ wave of the pneumocardiogram. Typically the greatest effect of loading change was during reduction of circulating volume when both the PnCG and dPn/dt IJ waves decreased to about 60% of control levels. This decrease demonstrates a significant dependence of the pneumocardiogram on cardiac preload. In the chemically denervated animals there was similar dependence on volume loading and a suggestion of an influence exerted by increased afterload. These data are typical of the loading dependence of most indices that measure heart function, including maximum blood acceleration,[15] maximum rate of rise of left ventricular pressure,[15,19] velocity of circumferential ventricular fiber shortening (V_{cf}),[20] and systolic time intervals.[21] The advantage of the pneumocardiogram is that it is noninvasive, as are systolic time intervals, and needs only one measuring transducer. A more complete discussion of its monitoring prospects is available elsewhere.[9]

ACKNOWLEDGMENTS

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WEDGE PRESSURE MEASUREMENT

The effect of the vertical height of the pulmonary wedge catheter in the lung on the pulmonary wedge pressure-left atrial relationship was studied during positive end-expiratory pressure (PEEP) ventilation in oleic acid-induced pulmonary edema. Pulmonary wedge catheters were placed above and below the left atrium in normal dogs and in dogs with oleic acid-induced edema. Wedge pressure and left atrial pressure were measured simultaneously during PEEP ventilation (range, 0 to 30 cm H_2O PEEP). Pulmonary wedge catheters below the left atrium correctly recorded left atrial pressure and change in left atrial pressure at all PEEP's studied. Pulmonary wedge catheters above the atrium consistently recorded pressures higher than the normal left atrial pressure. They did not correctly respond to increases in left atrial pressure until it was increased to a value higher than the initial upper pulmonary wedge pressure. Pulmonary arterial catheters, when properly placed, should be reliable indicators of left atrial pressure during positive-pressure ventilation in normal and edematous lungs. *(Tooker J, Huseby J, Butler J: The effect of Swan-Ganz catheter height on the wedge pressure-left atrial pressure relationship in edema during positive-pressure ventilation Am Rev Resp Dis 117:721-725, 1978)*

Comparison of Laryngeal Pathology Following Long-Term Oral and Nasal Endotracheal Intubations

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A study was undertaken to determine the incidence and type of laryngeal injury following long-term oral and nasal endotracheal intubation. Seventeen intensive care unit patients who were intubated from 5 to 9 days were studied. Seven patients had orotracheal intubation; 10 were intubated through the nose. Within 24 hours following extubation or tracheostomy, fiberoptic bronchoscopy was performed to evaluate the extent of laryngeal injury. A grading system used to quantify the degree of injury was based upon presence or absence of: vocal cord ulceration, vocal cord cratering and maceration, ulceration of the arytenoid or corniculate cartilages, ulceration of the glottic surface of the epiglottis, ulceration of the proximal posterior tracheal wall, supraglottic edema, and glottic closing abnormalities.

A standard lateral skull radiograph was performed on patients who had been nasally intubated. Anatomical measurements were calculated from these radiographs in an attempt to correlate extreme variations from the normal with an increased incidence of laryngeal pathology. These measurements included calculation of palatal length and angulation and the position of the first cervical vertebra in an anterior-posterior position.

Although laryngeal damage was found following intubation by either route, our results showed that long-term oral endotracheal intubations were associated with injury approximately twice as often as were nasal intubations. We found no evidence that palatal length and angulation or position of the first cervical vertebra affected the incidence or type of laryngeal injury following nasotracheal intubation. We recommend nasal intubation over oral intubation in adult patients requiring long-term pulmonary support in whom there are no contraindications to nasotracheal intubation.

Key Words—LARYNX, postintubation complications. INTUBATION, endotracheal, complications.

ANESTHESIOLOGISTS are frequently involved with the management of patients requiring prolonged endotracheal intubation. Reports of complications in such cases describe lesions of the larynx and trachea.[1-8] We have found that serious tracheal lesions such as tracheal ulcerations and tracheoesophageal fistulas are for the most part preventable with careful management of the upper airways and regulation of endotracheal-tube cuff pressure. However, laryngeal lesions occur despite diligent efforts to avoid them by prophylaxis, prompt identification, and proper management.

We have studied laryngeal lesions secondary to both oral and nasal intubations and compared the resultant pathology from each. Also, we have used measurements from lateral skull roentgenograms in an attempt to correlate hard palate length and angulation and the position of the first cervical vertebra with the incidence and type of laryngeal pathology secondary to nasal intuba-

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tion. By comparing the relative safety of nasal and oral routes for long-term endotracheal intubation we hoped to determine the laryngeal pathology expected from nasal intubation and thereby minimize it by initially selecting proper endotracheal tubes and by encouraging our surgical colleagues to perform tracheostomy at an appropriate time.

MATERIALS AND METHODS

Seventeen adult patients in the medical-surgical and neurosurgical intensive care units were included in this study. All patients were suffering from acute illness or injury with respiratory failure. All patients were intubated, either nasally or orally. Polyvinyl tubes with high-volume, low-pressure cuffs were used in all intubations. Males were intubated orally with 8.5-mm or 9.0-mm endotracheal tubes and nasally with 8.0-mm to 8.5-mm tubes. Females were intubated orally with 8.0-mm tubes and nasally with 7.5-mm to 8.0-mm endotracheal tubes. The patients were intubated for 5 to 9 days, after which they were either extubated or underwent tracheostomy. Within 24 hours after extubation or tracheostomy, the upper airway was examined with a fiberoptic bronchoscope to determine the extent of injury to the larynx and trachea caused by the intubation. The laryngeal injuries were graded in severity from zero to 8, zero representing no injury. The following pathological changes (most of which are diagramed in fig 1) each added one grade until a maximum of 8 was reached:

1. Superficial vocal cord ulceration

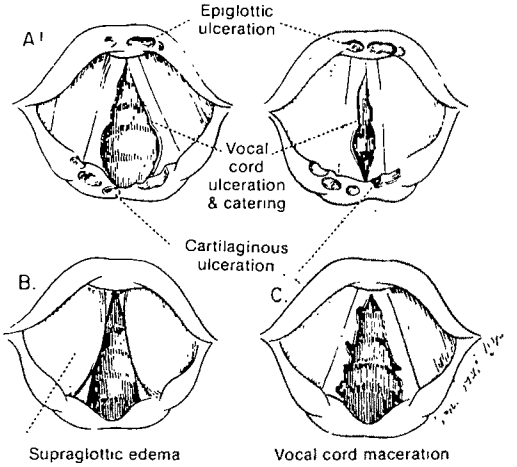


FIG 1. Diagrammatic representation of vocal cord injury

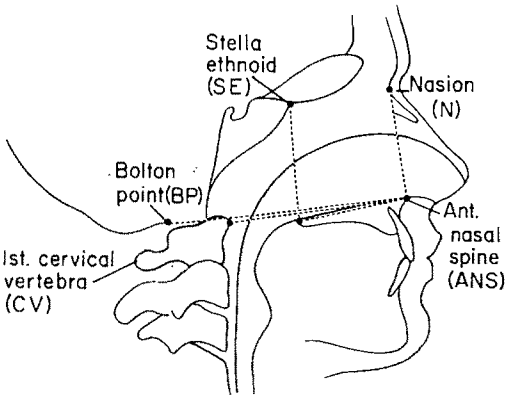


FIG 2. Cephalometric measurements

2. Vocal cord cratering

3. Maceration of vocal cords

4. Ulceration of arytenoid or corniculate cartilages

5. Ulceration of the glottic surface of the epiglottis

6. Ulceration of the proximal posterior tracheal wall approximating the glottic opening

7. Supraglottic edema

8. Functional impairment of glottic closing mechanism

Other complications attributed to nasal intubation, such as sinusitis, nasal septum damage, eustachian tube edema, bacteremia, and epistaxis, were not evaluated in this study. When physically able after nasal endotracheal intubation, all patients were transported to the radiology department for a cephalometric analysis by a standardized lateral skull roentgenogram. Various measurements of bony landmarks relative to the path of the nasal endotracheal tube were analyzed. These measurements included (fig 2):

1. ANS-BP: Distance from the anterior nasal spine to Bolton point (the highest point in the concavity behind the occipital condyle)

2. ANS-PNS: Distance from the anterior nasal spine to posterior nasal spine

3. ANS-N: Distance from the anterior nasal spine to nasion (the junction of the internasal suture with the nasofrontal suture)

4. ANS-CV: Distance from the anterior nasal spine to anterior body of the first cervical vertebra

5. PNS-SE: Distance from the posterior nasal spine to sella-ethmoidal junction.

Using these measurements, ratios were then determined to correlate and predict the extent of laryngeal damage from long-term nasal endotracheal intubation. These ratios included:

1. $\frac{\text{ANS PNS}}{\text{ANS-BP}}$

2. $\frac{\text{ANS-N}}{\text{PNS-SE}}$

3. $\frac{\text{ANS-CV}}{\text{ANS-BP}}$

The theoretical effects of varying ratios are demonstrated in fig 3.

Intubations in this study were carried out by surgical or anesthesia house-staff. Patients were not included for study until after their intubations. All fiberoptic bronchoscopic examinations were performed by the authors in an effort to standardize the grading procedures as much as possible. To eliminate personal bias, photographs of the pathology of each case were graded by the authors without knowledge of which route of intubation had been used.

RESULTS

Table 1 summarizes patient data and the scope of the pathology. Both oral and nasal intubations averaged 6.7 days, with a range of 5 to 9 days. Using our grading criteria, the severity of laryngeal injury was calculated for both groups. The patients who had undergone oral endotracheal intubation averaged 4.6; those intubated nasally aver-

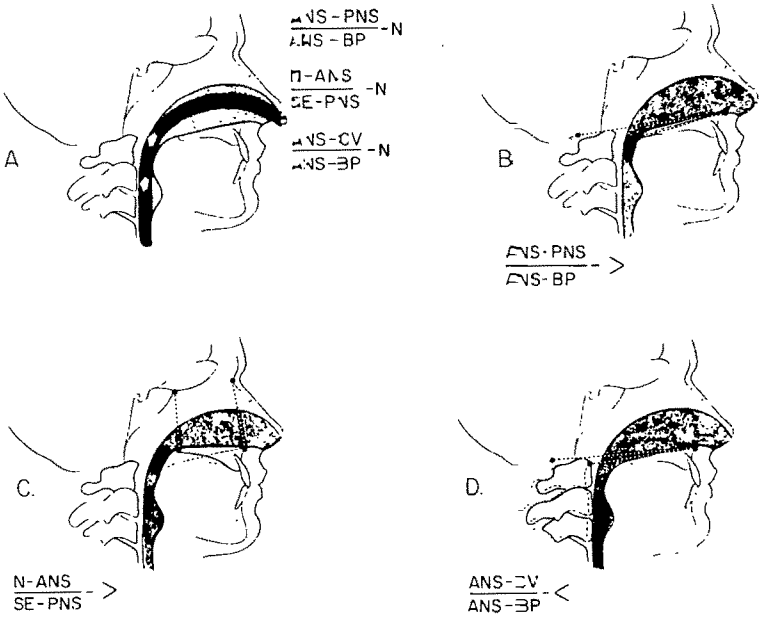


FIG 3. Theoretical effect of varying ratios
(a) Normal condition

(b) $\frac{\text{ANS-PNS}}{\text{ANS-BP}}$ Larger ratio represents increased palatal length as compared to sagittal facial length. This longer palatal length might increase the fulcrum effect of the nasal endotracheal tube on the posterior larynx and cause greater injury.

(c) $\frac{\text{N-ANS}}{\text{SE-PNS}}$ Larger ratio represents increased palatal angulation in a cephalocaudal direction and theoretically might produce more trauma due to the fulcrum effect.

(d) $\frac{\text{ANS-CV}}{\text{ANS-BP}}$ The smaller the ratio, the more anteriorly placed is the cervical vertebra. The increased pressure on the nasal endotracheal tube might tend to increase posterior laryngeal injury. Measurements were made to the 1st vertebral body, but its position corresponds to the position of the 2nd and 3rd vertebral bodies, which approximate the laryngeal area.

TABLE 1
Pathologic Changes Associated With Oral and Nasal Intubation

Route of intubation	Days intubated (mean)	Grade* (mean)	Vocal cord			Cartilaginous damage	Ulceration epiglottis	Proximal tracheal wall ulceration	Closing mechanism	Supraglottic edema
			Ulceration	Cratering	Maceration					
Oral intubation, 7 pts	6.7	4.6	100%	100%	14%	85%	57%	14%	28%	57%
Nasal intubation, 10 pts	6.7	2.4	100%	70%	20%	10%	0	0	10%	30%

*See text for description of grading criteria

aged 2.4. Patients intubated orally for over 5 days scored a 4 to 7 on the grading system. The severity of laryngeal injury in nasally intubated patients ranged from 1 to 5 on the grading scale, although only 3 patients scored 3 or more.

All patients in this study demonstrated vocal cord ulceration. All patients intubated orally and 70% of the patients intubated nasally exhibited vocal cord cratering posteriorly. The remainder of the lesions found were predominantly in patients intubated orally. Arytenoid and corniculate tubercle ulceration, ulceration of the epiglottis, and supraglottic edema were frequently seen in orally intubated patients but were less often observed in nasally intubated patients. Some of the clinical pathologic changes are seen in fig 4.

The results of the cephalometric measurements and ratios derived from them are presented in table 2. The cephalometric measurements found in our patients are compared with those published in the literature.[9] Published measurements of ANS-CV and ANS-BP distances are not available in the literature. Table 2 also reports the cephalometric ratios that we calculated retrospectively to predict degrees of laryngeal damage secondary to prolonged nasal endotracheal intubation.



FIG 4. Photograph of injured larynx, showing vocal cord ulceration, cratering, maceration, and cartilaginous edema

DISCUSSION

Studies of the incidences and types of laryngeal damage secondary to endotracheal intubation are restricted solely to observations following oral endotracheal intubation.[6,8,10,11] Our study of laryngeal pathology following extubation compares oral with nasal endotracheal intubations, as evaluated by fiberoptic bronchoscopy. All patients in this study were intubated with the same type of nonreactive, plastic disposable endotracheal tube with a curvature 35 cm in diameter.

Several published reports of laryngeal complications following prolonged endotracheal intubation emphasize duration of intubation as a major determinant of the severity and incidence of laryngeal injury.[5,8,10,11,13] Since microscopic surface mucosal alterations are found after 2 hours[12] of intubation and macroscopic changes after 6 hours,[10] laryngeal damage can be expected to and does increase in severity as the duration of intubation increases. In our patients, all of whom were intubated from 5 to 9 days, the route of intubation was also a significant factor in determining the severity of laryngeal injury. Nasal endotracheal tubes produced laryngeal injury approximately half as often as oral endotracheal tubes did. We believe that nasal tubes produce more stability and are less affected by patient head movement. Nasal endotracheal tubes are usually 0.5 mm to 1 mm smaller in diameter than oral endotracheal tubes and, therefore, also have less potential for the production of laryngeal injury because of their smaller size. The majority of patients intubated in this study exhibited ulceration and cratering, which are due to the pres-

TABLE 2
Study Population*

	Male	Female	Male	Female
ANS-PNS*	60.0†	52.4	61.6 ± 3.7	57.0 ± 4.4
N-ANS	56.3	55.2	59.6 ± 3.9	55.7 ± 2.1
SE-PNS	53.5	51.7	54.7 ± 4.4	49.6 ± 3.3
ANS-CV	97.1	84.7	——	——
ANS-BP	138.8	122.5	——	——

*See text for definitions of anatomic landmarks
†Mean distances in mm

CEPHALOMETRIC RATIOS—AVERAGES
Study Population

	Male	Female	Combined
$\frac{\text{ANS-PNS}}{\text{ANS-BP}}$	0.44	0.43	0.43
$\frac{\text{N-ANS}}{\text{SE-PNS}}$	1.05	1.06	1.05
$\frac{\text{ANS-CV}}{\text{ANS-BP}}$	0.71	0.69	0.70

sure the endotracheal tube exerts on the posterior larynx. This pressure is caused by the lever action of the tube as it bends over the tongue in an oral intubation and over the palate in a nasal intubation. The ulcerations of the corniculate tubercles, arytenoid cartilages, epiglottis and posterior tracheal wall, the supraglottic edema, and the incomplete closing mechanism that we found are most likely caused by movement of the endotracheal tube in a patient orally intubated. Movements of the tongue, mandible, and head contribute to this increased laryngeal irritation.

Motor activity of the larynx should also influence the degree of injury. With increased activity of the vocal cords and movement against the endotracheal tube, ulcerative lesions of the medial surface of the arytenoid cartilage and posterior vocal cords become more frequent. In our study, however, only one patient intubated nasally demonstrated cartilaginous damage, but 85% of the orally intubated patients had corniculate and arytenoid cartilage damage. Vocal cord movement is not particular to oral or nasal endotracheal intubations. Perhaps nasal intubation provides a degree of stability to tube placement that offsets the effects of cord movement.

Our observations of laryngeal injury were made within 24 hours following extubation or tracheostomy. We have found that follow-up examination reveals healing of most of the laryngeal injury. However, severe cartilagenous injury may result in permanent vocal cord cratering and dysphasia. Severe edema of the subglottic area and ulceration of the vocal cords may result in laryngeal stenosis and polyp formation, respectively.

The second phase of this study involved cephalometric analysis of the nasally intubated patients and calculation of ratios involving palatal length and angulation and the anterior-posterior position of the first cervical vertebra. When compared to the average ratios, both in our study population and from published measurements, we found no significant relationship between either palatal length, angulation, or position of the cervical vertebra and the degree of laryngeal injury. The standard 35-cm diameter of the endotracheal tube curvature is apparently sufficient to balance the effect of anatomical variability in the development of posterior laryngeal pressure.

Although laryngeal damage was found after prolonged intubations by either route, our study demonstrates that long-term oral

endotracheal intubation is associated with significantly more frequent and more severe laryngeal injury than is nasal intubation. We found no evidence that varying differences in palatal length and angulation and the position of the first cervical vertebra are related to greater or lesser frequency or degree of laryngeal injury. Therefore, in terms of laryngeal complications we recommend nasal intubation in adult patients requiring long-term pulmonary support via an endotracheal tube in whom there is no contraindication to nasotracheal intubation.

ACKNOWLEDGMENT

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INSULIN USE AS CARDIAC INOTROPIC AGENT

Insulin was administered to 2 patients whose diminished myocardial contractility made it difficult to terminate cardiopulmonary bypass. In both instances, bypass was successfully terminated shortly after the insulin injection. These clinical observations led to experiments under the controlled conditions provided by the isolated, working rat heart preparation. The recovery of contractility after 30 minutes of severe ischemia was assessed in all 11 control and 11 insulin-treated hearts. Myocardial performance, as judged by the product of heart rate and peak systolic blood pressure, was significantly greater in the insulin-treated hearts. These clinical observations and experimental findings suggest the need for more extensive study of the potential value of insulin in treating depressed contractility after prolonged myocardial ischemia. *(Muller JE, Mochizuki S, Koster JK, et al: Insulin therapy for depressed myocardial contractility after prolonged ischemia. Am J Cardiol 41:1215-1221, 1978)*

An Evaluation of Liquid-Crystal Thermometry as a Screening Device for Intraoperative Hyperthermia

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Disposable liquid-crystal temperature-trend indicators were evaluated under clinical conditions that simulated the development of intraoperative hyperthermia during anesthesia. Comparison was made to forehead thermistors for rapidity, accuracy, and linearity of response as well as correlation with esophageal and rectal thermistor recordings. The liquid-crystal monitors were comparable to the forehead thermistors in both rapidity and linearity of response, but not in accuracy. A linear correlation existed with the esophageal thermistor temperatures. Correlation with the rectal temperatures was not as exact. It is concluded that liquid-crystal thermometers may adequately serve as screening devices for intraoperative hyperthermia.

Key Words — TEMPERATURE, monitoring. MEASUREMENT TECHNICS, liquid-crystal thermometry.

THERE is little justification for the absence of continuous clinical thermometry during major surgery in this day and age and much to recommend its implementation. The hazards of inadvertent hypothermia and malignant hyperthermia are well known, and early recognition of temperature abberations can reduce anesthetic morbidity and mortality.

Ideally all patients undergoing anesthesia, no matter how brief the procedure, should have their temperatures monitored continuously both during the surgery and in the recovery phase. Presently, however, continuous clinical thermometry is often cumbersome, the electronic equipment being fragile, expensive, and at times hazardous to the patient.[1] Thermocouple or thermistor thermometry is rarely carried over into the recovery phase, even if employed during the anesthetic except in the most major of surgical undertakings.

Recently, however, with the introduction into clinical practice of Mylar® strips impregnated with microencapsulated cholesteric liquid crystals, a new means of continuous temperature monitoring became available. One readily available type* is de-

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signed to be applied to the forehead and has a Fahrenheit scale ranging from 86 to 102 in 2-degree increments. Intermediate temperatures in 0.5-degree increments are interpolated by comparison of the observed color with a reference guide. They are intended to serve only as temperature-trend indicators that would signal the need for more conventional temperature monitoring.

While mild intraoperative hypothermia may be the more likely occurrence in the anesthetized adult patient, hyperthermia, malignant or otherwise, is more ominous.[2] Malignant hyperthermia is possible with even the briefest anesthetic. We therefore undertook a study of these temperature-trend indicators in a clinical setting that simulated the development of intraoperative hyperthermia under anesthesia. The following factors were assessed: (1) accuracy of response; (2) linearity of response; and (3) rapidity of response. In conjunction with this, we re-examined the known correlation between core temperatures and skin temperatures under hyperthermic conditions.

METHOD

We chose to evaluate liquid-crystal temperature-trend indicators in 6 male patients undergoing whole-body hyperthermia as part of the treatment of metastatic cancer. Whole-body hyperthermia is currently undergoing evaluation at several centers to determine its efficacy as an adjuvant mode of therapy in the treatment of various neoplasms. Ongoing studies by Henderson and Pettigrew[3] in Scotland have demonstrated the feasibility and safety of this mode of therapy. Informed consent was obtained from all patients undergoing whole-body hyperthermia, and formal institutional approval was obtained.

In our protocol, core temperatures of patients are raised to 41.8 C over a period of approximately 2 hours. Once this temperature is achieved, it is maintained for 4 hours. The hyperthermia is induced by means of a high-flow, low-volume water-perfusion suit through which water, initially at 43 C, is passed. The water-perfusion suit is then encased within a specially constructed thermal sleeping bag which permits only the patient's head and neck to be exposed.

The psychological and physical discomfort of confinement for prolonged periods in a stressful thermal environment as well as pre-existent cancer pain necessitates use of continuous analgesia and sedation. A continuous low-dose ketamine infusion[4] (25 μg/kg/min) was used in these patients.

Specially designed, electrically isolated preamplifiers utilizing thermistor probes* provided a continuous digital display of the esophageal, rectal, and forehead temperatures. These units were calibrated daily against a precision, expanded-range mercury thermometer with an absolute accuracy of 0.1 C traceable to the National Bureau of Standards. Over the scale range of 37 to 42, maximum error for these units was 0.1 C (relative accuracy $\pm 2\%$ of scale range). Response time over the scale range to a 1 C stepwise change in temperature was less than 60 seconds. Information from the various thermistors is automatically fed into a microprocessor control unit which adjusts the perfusate temperature to raise the patient's temperature to 41.8 C and maintain it there for 4 hours with only ± 0.1 C variation.

The esophageal thermistor probe was placed in the lower fourth of the esophagus below the level of the pulmonary vessels with radiographic confirmation. The rectal probe was inserted to a depth of 10 cm and the forehead skin thermistor was carefully isolated from the influence of the ambient environment by means of plastic foam insulation. The liquid-crystal plastic strip was affixed to the forehead adjacent to the skin thermistor. Relative humidity in the room was maintained between 30 and 40% while the ambient room temperature was held between 24 and 27 C.

Recordings of rectal, esophageal, and skin thermistor temperatures were made every 5 to 10 minutes during the 2-hour period in which the patient's temperature was being increased from 37 to 41.8 C. An independent observer at the same time read the liquid-crystal temperatures. Temperatures were interpreted according to the reference chart supplied with the liquid-crystal monitors. In all cases the most brightly illuminated numerals were read. The same observer read all liquid-crystal temperatures so that the same subjective interpretation applied in all cases. The assembled data were fed into a Tektronix 4051 Graphics Calculator System† and were analyzed with their graphics and statistical software programs.

*Series 400 probes, Yellow Springs Instruments, Yellow Springs, Ohio 45387

†Tektronix, Inc., Beaverton, Oregon 97077

RESULTS

Initially the esophageal thermistor temperatures of all 6 patients were plotted against the forehead thermistor readings to determine the relationship between the 2 measurements in this group of patients and to determine if the skin thermistor temperature adequately tracks the esophageal temperature changes. The plot of this relationship is shown in fig 1. Individual data points are represented by "•"s, the linear-regression line being the solid black line. The line of agreement which indicates equivalent values is the lighter, serrated line. Linear-regression analysis in this case showed an r^2 correlation coefficient of 0.88 ($p<0.05$) with a slope that essentially parallels the line of agreement.

A plot of liquid-crystal temperatures in degrees Fahrenheit (with Centigrade conversion) against forehead thermistor temperatures in degrees Centigrade is shown in fig 2. Here the linear regression analysis produced a regression line with an r^2 correlation coefficient of 0.94 ($p<0.05$), and the individual data points were well clustered about the regression line. While the response is remarkably linear, there is some inaccuracy so that the regression line and the line of agreement are not congruent. The slope of the regression line is less than that of the line of agreement, but the Y intercept is greater. This indicates, as shown here, that the 2 lines will intersect. The intersection occurs at approximately normal body temperature.

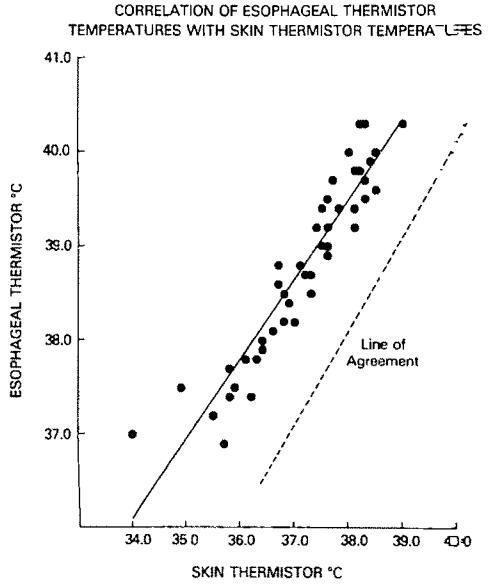


FIG 1. Linear-regression analysis: slope 0.85, Y intercept 7.23, r^2 correlation coefficient 0.88, $p<0.05$

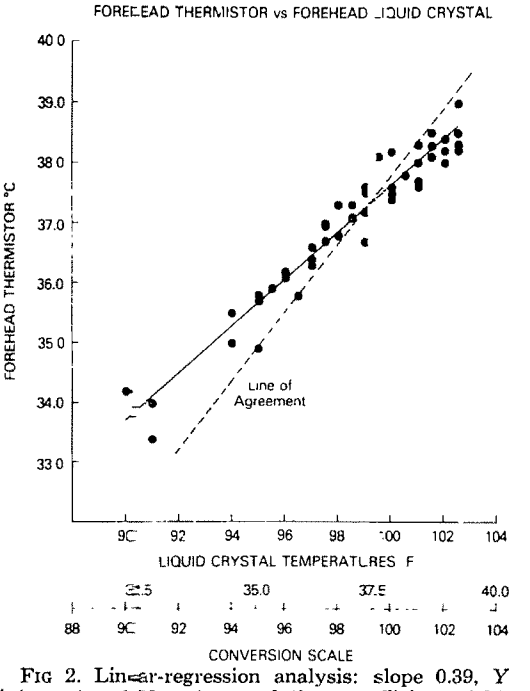


FIG 2. Linear-regression analysis: slope 0.39, Y intercept −1.50, r^2 correlation coefficient 0.94, $p<0.05$

A plot of the esophageal thermistor temperatures against the forehead liquid-crystal readings is shown in fig 3. Regression-line analysis in this case showed an r^2 correlation coefficient of 0.97 ($p<0.05$), with a slope essentially parallel to that obtained when the liquid-crystal devices were plotted against skin-thermistor temperatures.

The correlation between elevations in rectal temperatures and forehead liquid-crystal readings was not as exact. The correlation coefficient for the linear-regression line (fig 4) was only 0.83 ($p<0.05$), with a greater scatter of the data points about the regression line. An exponential curve fit for the same data was not any better; the r^2 correlation coefficient was again 0.83 ($p<0.05$).

The response times to detect the onset of hyperthermia in each patient were determined from the minutes elapsed after entry of the heated water into the perfusion suit until the forehead thermistors showed a 0.3 C rise or the liquid-crystal monitors were interpreted as showing a 0.5 F elevation. The smallest change discernible on the liquid-crystal monitors is 0.5 F and is approximately equivalent to 0.3 C. The small error of 0.05 C in conversion (0.5 F = 0.28 C)

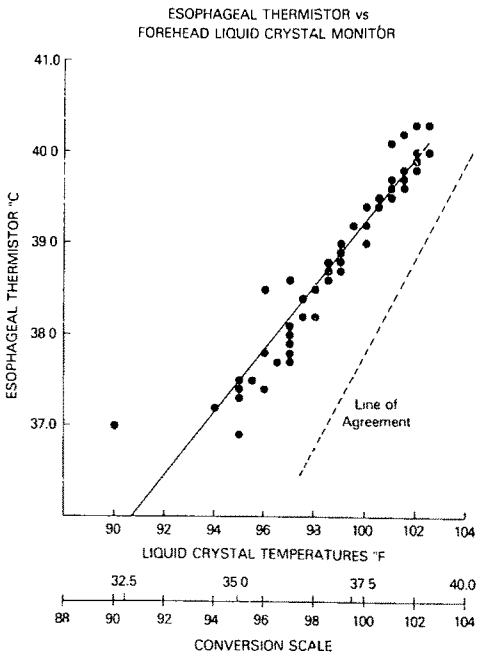


FIG 3. Linear-regression analysis: slope 0.34, Y intercept 4.40, r^2 correlation coefficient 0.97, $p<0.05$

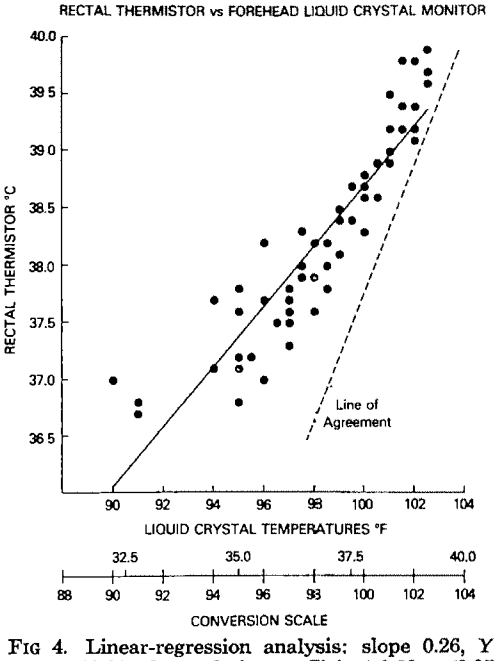


FIG 4. Linear-regression analysis: slope 0.26, Y intercept 12.21, r^2 correlation coefficient 0.83, $p<0.05$

was not corrected for, as it was beyond the sensitivity of the instruments. Theoretically, with a heating rate of approximately 2.5 C per hour this error would affect response time by less than 30 seconds.

As can be seen in the table, there was no appreciable difference between the response times of the 2 modes of thermometry in detecting a temperature elevation. Subsequent laboratory determinations recorded response times of less than 60 seconds for a 2 F (1.1 C) stepwise change in temperature over the scale range (86 to 102 F) with these liquid-crystal monitors.

TABLE
Response Times for Detecting Onset of Hyperthermia

Patient	Forehead liquid crystal (min)	Forehead thermistor (min)
1	5.0	5.0
2	12.0	12.0
3	25.0	25.0
4	41.0	32.0
5	24.0	24.0
6	...	...
Mean ± SEM	21.4 ± 13.8	19.6 ± 10.9

Difference not significant at $p<0.20$ level

DISCUSSION

Even when systemic temperatures remain constant throughout the body, skin temperatures can vary several degrees from one area to another. The range is usually from 30 to 35 C. Exposure to ambient temperatures, the covering of fat over the capillary beds, and local circulatory patterns are just a few of the factors that influence temperatures over the surface of the body. The skin temperature is therefore a result of a balance between the heat supplied by the circulation and the cooling of skin by conduction, convection, radiation, and evaporation. Thus, skin temperature is a function of many independently assorted variables. It can even be perturbed by the type of device chosen for measurement.

Our study shows that forehead skin temperatures reflect esophageal temperatures in a reasonably linear fashion. In fig 1, the slope of the linear regression was essentially parallel to the line of agreement. The Y intercept of 7.23 is a reflection of the fact that skin temperature is normally several degrees cooler than esophageal temperature. The forehead is an easily accessible monitoring site with minimal subcutaneous fat. In addition, with an increase in core temperature due either to exogenously applied heat or endogenously generated heat, there is an increase in cardiac output coupled with cu-

taneous vasodilatation.[5] In general, skin temperatures are an index of cutaneous perfusion.

Esophageal temperature accurately reflects intracardiac or core temperature provided there are no sudden heat losses or gains.[6] The esophageal temperature rapidly tracks intracardiac blood temperature, but it is critical that the esophageal probe be properly placed in the lower fourth of the esophagus beneath the pulmonary vessels and between the heart and the descending aorta.[7] This is the warmest and most stable location. Placement of the probe otherwise can result in an error of several degrees, and changes in the intracardiac or core temperature will not be reflected as rapidly.

Our data indicate that the agreement between the traditional skin thermistor and the liquid-crystal device placed on the forehead was excellent with respect to linearity. Rapidity of response in the clinical and laboratory trials was comparable to the thermistor probes. Maximum error was less than ±15% of the scale range for the liquid-crystal monitors.

Comparison of liquid-crystal temperature determinations with esophageal recordings showed that liquid-crystal temperature-trend indicators promptly reflect increases in temperature in a linear manner. The Y intercept of 4.40 is again a reflection of the fact that skin temperature is normally several degrees cooler than esophageal temperature.

As might be expected, correlation of liquid-crystal skin temperatures with rectal thermistor recordings was not as exact. Although rectal temperature is commonly monitored in clinical anesthesia, it is not a true representation of core temperature and is of little physiological importance. The rectum does not have thermal significance of its own and there are no thermal receptors in the rectum. It is far removed from the central nervous system and it is not located near any great vessels so it cannot be said to reflect intracardiac blood temperatures. No clear relationship exists between rectal temperatures and either vasomotor tone or sweating. In the anesthetized patient, rectal temperature and tympanic temperature, which reflects core temperature, often differ by wide margins.[8]

Liquid-crystal temperature-trend indicators have several advantages over thermistor or thermocouple probes when used for routine temperature monitoring during and after anesthesia. Included are the following advantages:

(1) Convenient and easily applied

(2) Readily accessible to the anesthesiologist

(3) Noninvasive and nonperturbing to the measuring site

(4) Self-contained and devoid of electronic circuitry

(5) Disposable, thereby eliminating risk of cross-contamination

(6) No electrocution or burn hazard

(7) Inexpensive (approximately $1.50 per monitor).

The disadvantages of liquid-crystal temperature trend indicators include the following:

(1) Subjective observer interpretation is required for measurement.

(2) The monitor cannot be interfaced with a recording system.

(3) Accuracy is less than that of thermistors.

These devices seem well suited to brief anesthetics for simple surgical procedures where temperature might not otherwise be monitored. A distinct advantage is that these monitors can be easily transferred to the recovery area with the patient. It is not expected that they would substitute for the more conventional means of temperature monitoring during major surgical procedures where many factors can affect cutaneous temperatures. Other potential applications of liquid-crystal temperature monitors include monitoring limb perfusion after vascular surgery and documentation of the onset of sympathetic blocks with accompanying increase in cutaneous perfusion.

While lacking the accuracy of thermistor thermometry, the linearity and rapidity of response of liquid-crystal temperature-trend indicators enable them to serve as practical screening devices for intraoperative hyperthermia. It remains to be demonstrated whether these monitors will function equally as well under hypothermic conditions where cutaneous vasoconstriction may produce large thermal gradients between core and skin temperatures. In either case, however, rapid or large fluctuations in temperature as indicated by these liquid-crystal monitors signal the need for more accurate and direct thermometry by traditional means.

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CORRECTION

"Cardiac Dysrhythmia Following Reversal of Neuromuscular Blocking Agents in Geriatric Patients" (Anesth Analg 57:186-190, 1978) contains an error. Due to a statistical error, the results concerning hypertensitive patients presented in table 2 were incorrectly stated to be significant at the 0.05 level. Actually, this is a statistically insignificant comparison between neostigmine and pyridostigmine.

Gastric Fluid pH in Patients Receiving Cimetidine

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Gastric fluid pH was measured immediately after anesthetic induction in 150 fasted adult patients with or without prior cimetidine. All patients had received morphine-atropine preanesthetic medication. Gastric fluid pH was above 2.5 in 39/50 patients (78%) receiving cimetidine 300 mg orally with 50 ml H_2O the evening before operation. The same dose of oral cimetidine but 60 to 90 minutes before anesthetic induction resulted in gastric fluid pH above 2.5 in 42/50 patients (84%). In contrast, gastric fluid pH was above 2.5 in only 20/50 patients (40%) not receiving cimetidine. We conclude that oral cimetidine administered 60 to 90 minutes before anesthetic induction is a practical way to increase gastric fluid pH above 2.5 in the majority of fasting adult patients.

Key Words — HISTAMINE, inhibition, cimetidine. GASTROINTESTINAL TRACT, stomach, gastric pH.

CIMETIDINE (Tagamet®), a histamine H_2-receptor antagonist, is a potent inhibitor of gastric acid secretion.[1] Conceivably, preoperative administration of cimetidine might increase gastric fluid pH and thus reduce the potential for acid pneumonitis should inhalation of gastric fluid occur during anesthesia. Indeed, cimetidine 300 mg orally increased gastric fluid pH to 7 in healthy volunteers within 1 hour.[2] This report describes an increased incidence of gastric fluid pH values above 2.5 at the time of anesthetic induction in fasting patients receiving cimetidine.

METHODS

One hundred and fifty adult patients (ASA 1-2) scheduled for elective operations at 0800 hours were studied. All had fasted for at least 7 hours before anesthetic induction. Intramuscular preanesthetic medication was with morphine (8 to 15 mg) and atropine (0.4 mg) 90 minutes before anticipated anesthetic induction. Patients were divided into the following study groups:

(1) Cimetidine, 300 mg orally at 2200 the evening before operation, 50 patients

(2) Cimetidine, 300 mg orally with 50 ml of H_2O at the time of IM preanesthetic medication, 50 patients

(3) Control, no cimetidine, 50 patients.

Immediately following anesthetic induction and tracheal intubation with thiamylal and succinylcholine, an 18 French gastric tube (sump type) was passed into the stomach. Gastric fluid was aspirated for volume measurement and pH determination (Corning pH meter and Beckman electrode).

Data were analyzed using the chi-square test or analysis of variance, and $p<0.05$ was considered statistically significant. Mean gastric fluid pH was determined using the hydrogen ion concentration represented by individual pH measurements.[3]

RESULTS

Patient age, weight, and measured gastric volume were similar in the 3 study groups (table 1). Cimetidine administration preceded anesthetic induction by 7.7 ± 0.2 hours (mean ± SE) in patients treated the evening before operation and by 85 ± 11

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TABLE 1
Patient Age, Weight, and Gastric Fluid Volume (Mean ± SE)

Group	Age (years)	Weight (kg)	Gastric fluid volume (ml)
Cimetidine (evening before operation, $n = 50$)	43 ± 5	73 ± 4	10 ± 5
Cimetidine (preanesthetic medication, $n = 50$)	49 ± 6	72 ± 5	18 ± 5
Control (no cimetidine, $n = 50$)	50 ± 5	74 ± 4	15 ± 6

TABLE 2
Percentage of Patients with Gastric Fluid pH Samples

Group	pH		
	Below 2.5	2.5-5.0	Above 5.0
Cimetidine (evening before operation)	22%* (11)	38% (19)	40%* (20)
Cimetidine (preanesthetic medication)	16%* (8)	24% (12)	60%*† (30)
Control (no cimetidine)	60% (30)	34% (17)	6% (3)

(n) = number of patients

* = $p<0.05$ vs control

† = $p<0.05$ preanesthetic medication vs evening before operation

TABLE 3
Gastric Fluid pH (Mean ± SE) Within Each Study Group

Group	pH		
	Below 2.5	2.5-5.0	Above 5.0
Cimetidine (evening before operation, $n = 50$)	1.8 ± .08	3.4 ± .4	6.1 ± .3
Cimetidine (preanesthetic medication, $n = 50$)	1.7 ± .09	3.4 ± .4	6.1 ± .4
Control (no cimetidine, $n = 50$)	1.7 ± .1	3.2 ± .3	5.5*

*Average of 3 patients

Mean pH was determined from the hydrogen ion concentration represented by each individual pH measurement.

minutes in patients receiving the drug at the time of IM preanesthetic medication.

Compared with control patients, the incidence of gastric fluid pH samples below 2.5 was reduced ($p<0.05$) by the administration of cimetidine either the evening before operation or with the preanesthetic medication (table 2). Likewise, compared with control patients, cimetidine increased ($p<0.05$) the incidence of gastric fluid pH samples above 5.0. However, cimetidine administered with the preanesthetic medication was more effective than when given the evening before (60% versus 40% of gastric fluid pH samples above 5.0; $p<0.05$). The incidence of gastric fluid pH samples between 2.5 and 5.0 was not different among study groups.

The average gastric fluid pH when patients within each study group were divided according to pH below 2.5, 2.5 to 5.0, and above 5.0 was not different in the 3 study groups (table 3).

DISCUSSION

The development of acid pneumonitis depends upon the pH and volume of inhaled gastric fluid. Gastric fluid pH below 2.5 and an inhaled volume exceeding 0.3 to 0.4 ml/kg are considered most likely to produce acid pneumonitis.[4] Sixty-three percent of fasted adult patients receiving morphine preanesthetic medication had a gastric fluid pH below 2.5 immediately following induction of anesthesia.[5] Neither the incidence of gastric fluid pH below 2.5 nor the measured gastric fluid volume was altered by the IM administration of atropine (0.4 mg) or glycopyrrolate (0.2 mg) 60 to 90 minutes before anesthetic induction.[5] In another re-

port[6] a larger dose of glycopyrrolate (0.4 mg) was more effective as only 34% of patients had a gastric fluid pH below 2.5. Since cimetidine is a potent inhibitor of gastric acid secretion, it seemed a logical drug to evaluate as a means to increase gastric fluid pH before anesthetic induction. Oral administration was chosen since an IM form is not available.

These data demonstrate that cimetidine 300 mg orally either the evening before or with the preanesthetic medication the morning of operation raised gastric fluid pH above 2.5 in 78 and 84% of patients, respectively. Gastric fluid pH was above 5.0 in about 50% of these patients. In contrast, without cimetidine, gastric fluid pH was above 2.5 in 40% and above 5.0 in only 6% of patients. More patients receiving cimetidine with the preanesthetic medication, rather than the evening before operation, had a gastric fluid pH above 5.0. This suggests that the effect of cimetidine administered the evening before operation was waning at the time of anesthetic induction.

The effect of cimetidine on gastric fluid volume is not known. Our data do not show a difference ($p<0.05$) in measured gastric fluid volume among the 3 study groups. However, complete emptying of the stomach with a gastric tube cannot be assumed. It is possible the gastric fluid volumes measured in our patients would not accurately reflect differences in volumes between study groups.

Adverse side effects from cimetidine as used in this study were not observed. However, headache, dizziness, and diarrhea have been described with more prolonged cimetidine therapy.[7] Agranulocytosis has been reported with cimetidine but a cause and effect relationship was not established.[8] The use of cimetidine in pregnant patients at term is attractive but the pharmacokinetics of this drug and possible effects on the newborn have not been studied.

An oral antacid 30 minutes before anesthetic induction also increased gastric fluid pH above 2.5.[5] In contrast to cimetidine, administration of an oral antacid contributed to an increased gastric fluid volume at the time of anesthetic induction.[5] Furthermore, effects of antacids on the tracheobronchial tree, should aspiration occur, are not known. If routine prophylaxis is to be considered, cimetidine, 300 mg orally with a small volume of H_2O about 90 minutes before anesthetic induction, is a practical way to increase gastric fluid pH above 2.5 in the majority of fasting adult patients.

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A Test of the Carcinogenicity of Enflurane, Isoflurane, Halothane, Methoxyflurane, and Nitrous Oxide in Mice

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We exposed Swiss ICR mice for 2-hour periods to 1/32, 1/8 and/or 1/2 MAC enflurane, halothane, isoflurane, methoxyflurane, or N_2O both in utero during the last 1/2 of pregnancy (4 exposures at 2-day intervals) and after delivery (24 exposures at 2-to-3-day intervals). Anesthetics were delivered in air or in O_2. Thus, 1973 mice were exposed and examined after 15 months of life for the development of neoplastic lesions. Neoplastic lesions (principally pulmonary adenomas, lymphomas, hepatocyte lesions, liver vascular lesions) were found in all treatment and control sets. There was no indication that a specific anesthetic or anesthetic dose was carcinogenic. Our results do not confirm the suggestion that isoflurane is a hepatocarcinogen, nor do our data suggest that the modern inhaled anesthetics pose a significant threat of carcinogenicity.

Key Words—TOXICITY, carcinogenicity. ANESTHETICS, volatile, halothane. ANESTHETICS, volatile, enflurane. ANESTHETICS, volatile, isoflurane. ANESTHETICS, volatile, methoxyflurane. ANESTHETICS, gases, nitrous oxide.

CONCERN regarding the potential of anesthetics to cause cancer has arisen from epidemiologic and animal evidence. Reports on the association of occupational exposure to trace anesthetic concentrations and the incidence of cancer have given conflicting results.[1-6] The ASA Ad Hoc Committee on the Effect of Trace Anesthetics on the Health of Operating Room Personnel found a significantly increased incidence of cancer in female but not male operating room personnel.[4] Further studies are being conducted by the American Society of Anesthesiologists in concert with the American Cancer Society. Preliminary results presented at the 1977 meeting of the American Society of Anesthesiologists showed an age-adjusted overall death rate from cancer for male anesthesiologists equal to or lower than that found with other physician specialists. Data from a far smaller group of female anesthesiologists also showed no excessive death rate from cancer (43%). However, the number of deaths (35) was too small to refute the earlier study by the ASA Ad Hoc Committee for female operating room personnel.

Studies in mice and rats have demonstrated that large doses of chloroform[7,8] or trichloroethylene[9] given by intragastric instillation produce neoplastic changes in kidney and/or liver. Since these anesthetics are no longer used as anesthetics in the United States, their carcinogenicity is important only in that it may indicate a potential in more modern anesthetics.

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Of immediate interest to us was the finding in a pilot study by Corbett that isoflurane (Forane®) administration to Swiss ICR mice during gestation and early life produced hepatic neoplasia.[10] Unlike the above tests of chloroform and trichloroethylene, isoflurane was given by inhalation. Corbett had tested isoflurane, an alpha chloroether, because other alpha chloroethers are carcinogens in animals[11-13] and man.[14,15] However, the alpha chloroether compounds which cause cancer (chloromethyl methyl ether and bis-chloromethyl methyl ether) are radically different from isoflurane. They are reactive compounds and are direct alkylating agents. Other alpha chloroethers (eg, alpha, alpha-dichloromethyl methyl ether) which are more stable compounds do not produce neoplasia in rodents.[12] Isoflurane is stable even in the presence of strong alkali or ultraviolet light.[16] Furthermore, unlike many anesthetics, isoflurane is minimally metabolized in animals[17] or man[18] and hence the chance of production of active radicals by this route would appear to be small. Since such radicals are thought to be essential to alterations in DNA produced by chemical carcinogens, it seemed peculiar to us that isoflurane should be a carcinogen. Of concern was the thought that if isoflurane were a carcinogen, then anesthetics which are metabolized to a greater extent (eg, halothane, enflurane, methoxyflurane)[17] would be more potent carcinogens.

The following experiment was designed for two purposes. One was to reproduce Corbett's experiment and the other was to compare the carcinogenic potential of isoflurane with that of other modern inhaled anesthetics. We did not repeat Corbett's experiment exactly because that study contained several methodological flaws. Test and control animals were treated differently in several ways which might have influenced the results. The controls were not put in the exposure chambers, were not given O_2 alone, were never deprived of H_2O and were not allowed to eat food exposed to anesthetic. Gross and microscopic tissue examinations were not done blindly. In addition, some control animals were taken from another study not done concurrently. These errors were avoided in the present study. In addition, we used more animals in both test and control groups and used higher concentrations of anesthetic for a longer period of time (eg, the highest dose-time administration in our study was 5 times as great as the highest dose-time administration used by Corbett).

METHODS

Time-dated pregnant Swiss ICR mice from Simonsen Laboratories (Gilroy, California) were received on the 9th day of pregnancy and were assigned to various treatment sets. Each mouse was housed in an individual 7-by-11.5-inch cage covered by a filter top to protect against the spread of airborne disease. The guidelines for animal care suggested by the National Cancer Institute were followed throughout the study[19] except for minor modifications.

Two-hour exposures to test or control gases were begun 11 days following impregnation and repeated on days 13, 15, and 17. The mice delivered after 19 to 21 days of pregnancy. Anesthetic administration was resumed 5 days following delivery, again on a 2-hour-per-day basis, 3 times per week with 1 or 2 days separating each exposure for a total of 28 exposures (4 in utero and 24 after delivery). Water and food were withheld from both experimental and control animals for each period of exposure plus the ensuing 2 hours.

The exposure chambers were maintained within 2° C of ambient temperature either by air conditioning or by use of a sufficiently high gas inflow. Carbon dioxide was removed by recirculation of chamber gas through CO_2 absorbant at a rate sufficient to maintain the average CO_2 at 0.3% or less. Absorbant was changed after every exposure. Each chamber was equipped with an individual flow/temperature compensated vaporizer for each agent to be tested.

Achieving the desired anesthetic concentration in a "square-wave" fashion for each treatment was accomplished by injecting a liquid loading dose followed by a continuous flow of agent. Confirmation of the actual concentrations was made with infrared, ultraviolet, or gas chromatographic analysis during the first 7 to 15 minutes, the middle hour, and the last ½ hour of every exposure.

Oxygen concentrations were maintained at one of two levels: 25 to 30% (air background or 85 to 100% (O_2 background). Oxygen and CO_2 concentrations were measured with a Pauling meter and infrared analyzer, respectively, at the same intervals as the anesthetic concentrations. To avoid an excessive use of anesthetic in O_2-anesthetic exposures, we flushed the chamber with O_2 for 5 to 10 minutes prior to introduction of the anesthetic. Chamber gases

were vented to the outside at the end of each exposure.

Three weeks following delivery the offspring were weaned from their mothers. The sex of the pups was determined, and males and females thereafter were caged separately in groups of 4 to 6 animals. Exposures of pups but not mothers were continued after weaning. After the final exposure at about 2½ months of life, the animals were weighed. Each mouse was labeled with one or more ear punches that identified the treatment set to which he or she belonged. The animals then were housed in groups of 3 to 4 per cage and weighed at 6, 9, 12, and 15 months of life.

In all, 25 sets of mice were exposed to air, O_2, or anesthetic in air or O_2. These 25 sets made up 2 major groups and 2 minor groups. The groups differed in the starting date for impregnation (usually a several month difference). They also differed in the O_2 concentration used in the gas which carried the anesthetics: groups 1 and 4 used pure O_2 as the vehicle whereas in groups 2 and 3 the background O_2 concentration was about 25%.

The aim of the 1st major group (O_2 background) was to determine the relative carcinogenicity of isoflurane, halothane, enflurane, and N_2O, each in a background of O_2. There were 3 sets each of isoflurane, halothane, and enflurane animals corresponding to 1/2, 1/8, and 1/32 MAC for these agents; 2 sets of N_2O animals corresponding to 1/2 and 1/8 MAC; and 2 control sets, one of which was exposed to air and the other to O_2. Thus, there was a total of 13 sets of mice in the 1st group.

For isoflurane, MAC was estimated to be 1.2% of an atmosphere; for halothane, 1.0%; for enflurane, 2%; and for N_2O, 1.5 atmospheres. These and subsequently stated MAC values are not necessarily those for ICR mice but rather are an average of MAC values for several species including man.[20] For the ICR mouse they tend to underestimate potency, especially for isoflurane, where the MAC actually is 0.6%.[21]

Our plan for the 1st group called for exposure of sufficient numbers of animals to permit a harvest of mice at both 9 and 15 months following delivery. We wished to harvest 80 mice of each sex from each control set; 60 mice of each sex from the 1/2 MAC sets; and 40 mice of each sex from the 1/8 and 1/32 MAC sets. These goals were partially met. We anticipated little attrition during exposure in the control sets or low-dose anesthetic sets and a higher attrition in the higher dose anesthetic sets. Accordingly, relatively fewer mothers were assigned to the low dose or control sets and larger numbers of mothers to the high-dose sets. In fact, the attrition rates were unrelated to anesthetic dose and we found that we had excess numbers of mice in the higher dose anesthetic sets. Conversely, we did not achieve our numerical goals in the control or low-dose sets. For undetermined reasons, significantly fewer control mothers given O_2 alone delivered pups in group 1. This low delivery rate was not seen in the control mothers exposed to O_2 in group 2 (see below). One other event limited the number of animals surviving the 1/2 MAC N_2O exposures. On one occasion an overdose of N_2O was administered with the resultant loss of several mice.

The failure to achieve all of our numerical goals was dealt with as follows. A second set of O_2 and air controls was obtained as part of the 2nd group (see below). We presumed that if these animals demonstrated an incidence of abnormalities similar to the sets in the 1st group that the sets could be combined (ie, O_2 with O_2 and air with air). Similarly, the 1/2 MAC N_2O study was repeated and comprises the 3rd group. Since we believed that 9 months probably was insufficient time for the development of neoplastic changes, where a set had fewer numbers than we wanted, we reduced the number harvested at 9 months in order to secure a number closer to our goals for 15 months. Finally, where the numbers of animals in a given set exceeded our goals, at the end of the exposure period the excess animals were discarded. However, where sufficient mice were available we kept 10 to 30% more than the numbers we wished to have at harvest since we assumed that 10 to 30% would be lost from various incidental causes (eg, infection, fighting, or malignancies).

The purpose of the 2nd major group (air background) was 3-fold: (1) to increase the number of control animals; (2) to learn whether O_2 as the background gas influenced the carcinogenicity of the potent anesthetics; and (3) to include methoxyflurane in the study of relative carcinogenicity (MAC estimated to be 0.25%). In group 2 the background gas for the sets given anesthetics was air supplemented with O_2 to maintain chamber O_2 at approximately 25%. Thus, there were 2 control sets (O_2

and air), 3 isoflurane and halothane sets (1/2, 1/8, and 1/32 MAC), and 1 enflurane and 1 methoxyflurane set (each 1/2 MAC) for a total of 10 sets.

The numbers of mice in the 2nd group saved following exposure were less than the numbers in the 1st group. Animals of both sexes were saved following exposure at 1/2 MAC, but only 2/3 as many females as males were retained. We kept a greater number of males because Corbett found hepatic neoplasia only in males.[10] We saved only male mice exposed to 1/8 or 1/32 MAC isoflurane or halothane. With the exception of the control sets, we made no 9-month harvests from the 2nd group of mice

The 3rd group consisted of 1 set of mice exposed to 75% N_2O with the balance O_2. Harvests of this group were made at both 9 and 15 months.

The 4th group consisted of 1 set of mice exposed to methoxyflurane in O_2. Only male pups from this set were kept and harvested at 15 months.

As anticipated, some animals died prematurely. During the first 9 months of life, 4% of animals died. No information from these animals was retrieved. After 9 months the animals were inspected twice daily on weekdays and once daily on weekends. Any dead mice were immediately examined as described below for the 9- and 15-month harvest.

At harvest the mice were identified by cage number and the identification as to set confirmed by examination of ear punch markings. Each animal was killed by exposure to 100% CO_2. The autopsy was done by a physician or technician who was unaware of the specific exposure experienced by the animal. The mice to be harvested on a given day were selected by a computer-generated scheme which randomly assigned animals from each set. Therefore on a given day each dissector received mice from most (if not all) of the sets, and the order of receipt was random. The tissues examined grossly included the eyes, oronasopharynx, tongue, mandibular lymph nodes, salivary glands, thyroid and parathyroid, larynx, trachea and bronchi, thymus, heart, lungs, sternum, esophagus, stomach, small and large bowel, rectum, pancreas, spleen, liver and gall bladder, kidneys, suprarenal glands, periaortic and mesenteric lymph nodes, gonads and associated tissues, uterus, bladder, and skin. Other tissues were not examined unless examination was indicated by the appearance of tumor. The lungs were excised and weighed and then inflated with 3 to 5 ml of 10% buffered formalin and stored in 10% buffered formalin. Liver, spleen, kidney, and reproductive organs were weighed and stored in 10% buffered formalin. Other tissues appearing to be abnormal were stored in formalin. After at least 3 days of storage, the lungs, liver, spleen, reproductive organs, and kidney were cut into 1-to-2-mm sections under a 7-to-40-power dissecting microscope and each side of each section was examined for evidence of neoplasia or other abnormalities. The sectioning was done by a physician who was unaware of the specific treatment received by any given animal except for group 4 specimens, where the treatment was known. Blinding for the examination of group 3 specimens was accomplished by intermingling group 2 and group 3 specimens. Any abnormalities were resected and stored separately.

Because of the importance attached to the results from the liver specimens, each sectioned specimen was examined by at least 2 and usually 3 physicians. Livers from group 4 mice were the only exception in that they were only examined once.

Slides were made of all abnormal tissues from all groups. Slides of all abnormal tissues except liver were examined by a board-certified veterinary pathologist.

The slides of abnormal liver tissue were examined separately by 2 board-certified human pathologists. Where either or both human pathologists believed a neoplastic lesion was or might be present, the slide was examined by a 3rd board-certified human pathologist. A diagnosis of neoplastic change in hepatocytes or liver vascular tissue was made when 2 or 3 of the pathologists agreed on such a diagnosis. Slides were examined using the same blind approach described above for sectioning.

Slides of kidney, liver, spleen, lung, and gonads from apparently normal areas (normal tissue survey) were made from the following group 2 animals: 38 to 40 males and females from each control set (total, 158 mice) and 16 to 22 males and females from each of the 1/2 MAC sets (total, 198 mice). In addition, slides were made of all spleens (spleen survey) obtained from the following sets of group 1 mice: O_2 and air controls and 1/2 MAC isoflurane, enflurane, halothane, and N_2O. These slides were exam-

ined by a board-certified veterinary pathologist.

Slides of all gross abnormalities from animals harvested at 9 months were examined by a human pathologist; and tissues from animals dying prematurely were examined by a veterinary pathologist.

Abnormalities found on microscopy were defined by the examining pathologist(s) and scored for a given animal either as present or absent. Statistical evaluations were made by chi-squared analysis. We accepted as significant any value of $p<0.05$.

Serum for viral studies was obtained from selected animals from each set in groups 1 and 2 at sacrifice. At the 9-month sacrifice, pooled samples from 4 mice of each set in group 1 were studied. At the 15-month sacrifice serum was obtained from 4 mice from each set of group 1 and group 2. These samples were obtained from 2 mice of each sex unless the treatment set contained only males. Microbiological Associates, 5221 River Road, Bethesda, Maryland 20016, assayed the serum for antibodies to pneumonia virus of mice (PVM), reovirus type 3, K, Theiler's encephalomyelitis (GDVII), Sendai, Polyoma, mouse hepatitis (MHV), mouse adenovirus (MAV), minute virus of mice (MVM), lymphocytic choriomeningitis (LCM), and ectromelia.

RESULTS

Exposure Characteristics — Chamber O_2, CO_2, temperature, and anesthetic levels remained within the limits set. All average anesthetic concentrations were within 10% of the values defined in methods and in all but 2 sets (1/8 MAC N_2O, group 1; and 1/2 MAC methoxyflurane, group 2) the average was within 4% of each value.

Delivery and Survival Characteristics— The percentage of impregnated mothers who delivered varied considerably between sets without any apparent correlation with anesthetic agent or dose (table 1). As indicated above, control mothers given O_2 in group 1 delivered fewer pups. In addition, the control air mothers had the 2nd lowest delivery rate. We have no explanation for these findings, which were not repeated in group 2, where the lowest delivery rate was seen in the 1/8 MAC isoflurane set.

The average number of pups per mother at weaning and the number surviving the subsequent exposures did not differ in any consistent fashion between sets in a given group (except for the 1/2 MAC N_2O set in group 1, which suffered from an inadvertent hypoxic episode). However, the average pup count per mother at weaning was less in group 2 than in group 1. Younger mothers have lower pup counts than mothers previously bred. Possibly the mothers for group 1 were "mature" breeders where those for group 2 were primigravida. The sex of animals surviving to weaning seemed unrelated to treatment. On average, 52.6% were males (2488 out of a total of 4726 mice).

Except for group 4 mice, only a few mice died between weaning and termination of the anesthetic exposures (table 1). For groups 1 through 3, the lowest percentage surviving this period was 97.5 (females, group 1). This percent is slightly but significantly less than the survival rate for females in group 2 (99.5%). All group 1, 2, and 3 males had significantly better survival rates than group 4 males (survival rate, 92.0%). However, it should be noted that *none* of the methoxyflurane-treated sets in group 2 died in the period between weaning and the termination of exposure. That is, the effect appeared to be related to group rather than methoxyflurane exposure. Alternatively, the combination of O_2 plus anesthetic was more noxious than anesthetic alone. The latter interpretation is supported both by the group 4 vs 2 or 3 and the group 1 vs 2 comparisons noted above.

Weight Gain—All groups gained weight following cessation of anesthetic exposure with the greatest gains occurring early in life and at a time when the standard laboratory diet was enriched by the addition of sunflower seeds and rolled oats (between 9 and 12 months in group 1; 6 and 9 months in groups 2, 3, and 4). The 1/2 MAC anesthetic dose was associated with slightly lower body weights at 2½ months with each sex. Group 1 1/2 MAC females weighed 5 (halothane) to 15 (N_2O) percent less than their O_2 control peers. Males weighed 8 (enflurane, isoflurane) to 12 (N_2O) percent less. Similar differences were seen in group 2, where the females were 1 (methoxyflurane) to 11 (enflurane) percent less than their air peers. Males were 1% greater than (methoxyflurane) to 11% less than (halothane) their control peers. This dose-related weight difference tended to disappear as the animals grew. Mice given 1/8 MAC or 1/32 MAC had weight gains comparable to control animals. At harvest after 15 months of life, the weights of animals or their organs

TABLE 1

Delivery and Survival During Exposures, Group 1

	% mothers who delivered	Average pup count/ mother at weaning	% weaned/mother		Total weaned/ group		No. saved for further exposure		No. surviving exposure at 2½ months	
			Male	Female	Male	Female	Male	Female	Male	Female
Control Oxygen	26.8	10.9	56.8	43.2	63	48	62	48	62	48
Control Air	62.5	10.1	48.2	51.8	122	131	122	130	118	128
Isoflurane 1/2 MAC	73.1	9.6	47.9	52.1	140	150	132	128	127	125
Isoflurane 1/8 MAC	70.3	10.6	50.5	49.5	97	95	96	84	95	79
Isoflurane 1/32 MAC	84.2	9.2	60.8	39.2	91	59	91	58	91	54
Halothane 1/2 MAC	83.3	10.7	54.2	45.8	216	182	144	138	144	135
Halothane 1/8 MAC	85.1	10.2	48.0	52.0	113	121	92	84	88	82
Halothane 1/32 MAC	75.0	10.2	58.3	41.7	95	68	95	68	95	68
Enflurane 1/2 MAC	92.7	10.8	54.0	46.0	221	188	156	137	156	137
Enflurane 1/8 MAC	85.2	9.5	52.1	47.9	114	105	96	84	96	83
Enflurane 1/32 MAC	89.5	9.8	54.5	45.5	91	76	91	76	87	75
N_2O 1/2 MAC	87.5	3.3	48.3	51.7	56	60	56	56	51	55
N_2O 1/8 MAC	81.5	10.4	57.5	42.5	131	97	92	88	90	81
Delivery and Survival During Exposures, Group 2										
Control Oxygen	85.1	7.3	52.2	47.8	166	152	166	148	162	146
Control Air	78.0	5.9	55.3	44.7	126	102	126	94	126	94
Isoflurane 1/2 MAC	75.7	6.6	50.3	49.7	93	92	72	48	72	48
Isoflurane 1/8 MAC	47.8	5.9	60.0	40.0	39	26	39	0	38	—
Isoflurane 1/32 MAC	88.5	6.6	56.6	43.4	82	63	48	0	48	—
Halothane 1/2 MAC	84.4	6.8	47.0	53.0	87	98	72	44	72	44
Halothane 1/8 MAC	91.7	6.1	47.4	52.6	64	71	48	0	48	—
Halothane 1/32 MAC	85.7	7.3	51.9	48.1	68	63	48	0	48	—
Enflurane 1/2 MAC	86.2	5.7	50.0	50.0	71	71	71	48	71	48
Methoxyflurane 1/2 MAC	80.0	4.7	45.1	54.9	32	39	32	39	32	39
Delivery and Survival During Exposures, Group 3										
N_2O 1/2 MAC	78.9	6.4	57.6	42.4	110	81	100	70	100	70
Delivery and Survival During Exposures, Group 4										
Methoxyflurane 1/2 MAC	60.0	6.7	46.6	53.4	75	86	75	0	69	—

revealed little effect of treatment. Group 1 female mice given N_2O tended to be smaller than their group 1 peers but the difference was slight and not significant. As expected, male mice weighed more than their female counterparts. Group 2 animals were consistently smaller than group 1 mice and this difference in overall body weight was reflected in the organ weights except for the kidneys, which weighed the same in both groups. Kidneys were consistently larger in male animals in both groups; spleens were larger in females.

Premature Deaths—As anticipated, mice died prematurely from a variety of causes, including fighting (males), disease, and malignancy. The incidence of death increased with the age of the mice. For group 1 no relationship of premature deaths to anesthetic treatment was apparent. In group 2 in the 3-to-9-month period of life the male animals treated with 1/2 MAC isoflurane experienced a higher premature death rate than other 1/2 MAC treated sets. In the 9-to-15-month period the only significant difference in group 2 sets was between males given 1/2 MAC isoflurane and 1/2 MAC halothane; again the isoflurane-treated animals had a higher death rate. This higher death rate was not associated with a higher incidence of neoplasia.

The autopsy rate was low for animals dying during the first 9 months of life, but was over 90% for the 9-to-15-month period. The results of the autopsies revealed no association of malignancy or other abnormality and a particular treatment set. Infection was the most common cause of death, with pneumonia, lung lymphoid hyperplasia, and epithelial hyperplasia/metaplasia often prominent. Lymphomas also were found as the probable cause of death in a minor but significant number of mice (14.8%). No treatment was associated with a significantly earlier development of neoplasia.

Results of the Harvest at Nine Months—A variety of abnormalities, including neoplasia, were found in the mice killed at 9 months. No consistent pathological pattern was associated with either treatment or control sets. The most frequently found neoplasm was pulmonary adenoma (table 2).

TABLE 2
Liver and Lung Tumors in Mice Harvested at 9 Months

		Male			Female		
	MAC	*N*	Liver	Lung	*N*	Liver	Lung
Group 1							
O_2 control	0	28	3.6(1)	0	24	0	8.3(2)
Air control	0	42	0	2.4(1)	59	0	3.4(2)
Isoflurane	1/2	58	0	5.1(3)	59	0	10.2(6)
	1/8	45	2.2(1)	6.7(3)	33	0	6.1(2)
	1/32	42	0	4.8(2)	8	0	0
Halothane	1/2	81	0	6.2(5)	61	0	4.9(3)
	1/8	37	0	0	36	0	2.8(1)
	1/32	45	4.4(2)	0	23	0	8.7(2)
Enflurane	1/2	70	0	8.6(6)	66	0	4.5(3)
	1/8	44	2.3(1)	2.3(1)	38	0	2.6(1)
	1/32	39	0	2.6(1)	31	0	3.2(1)
N_2O	1/2	25	0	4.0(1)	26	0	0
	1/8	41	0	2.4(1)	38	0	0
Group 2							
O_2 control	0	54	0	7.7(4)	53	0	11.3(6)
Air control	0	49	0	4.1(2)	30	0	0
Group 3							
N_2O	1/2	49	0	8.2(4)	31	0	3.2(1)

N = number of mice

The liver lesions were all of the hepatocyte variety while the lung lesions were pulmonary adenomas. The number preceding the parentheses indicates the percentage of animals displaying a particular tumor. The number in parentheses indicates the number of mice displaying that tumor.

There was no significant difference between treatments. The highest incidence appeared in the group-2 female O_2 controls (11.5%), followed by the group-1 1/2 MAC isoflurane females (10.2%); the group-1 1/2 MAC enflurane males (8.6%); and the group-1 female O_2 controls (8.3%). Only 2 other neoplasias were found: a perivascular lymphoma in a control O_2 male and a bowel fibrosarcoma in a male mouse that received 1/32 MAC isoflurane.

Five hepatocyte lesions were discovered in group 1 males. No relationship to treatment or dose was apparent. Although no hepatocyte lesions were found in female mice, the difference from males was not significant.

Results of the Harvest at Fifteen Months

Lungs—Microscopic examination revealed both neoplastic and infectious changes, again without a consistent relationship to treatment. Pulmonary adenomas were the most frequent tumor in the lung (tables 3 and 4). Group-1 female mice given N_2O 1/2 MAC (but not 1/8 MAC) had a significantly higher incidence of pulmonary adenomas than their air control peers. Similarly, group-2 male mice given 1/2 MAC isoflurane or halothane had a significantly higher incidence of pulmonary adenomas than air control male mice. There was no significant difference with halothane and isoflurane at other dose levels. A similar comparison for halothane or isoflurane in group 1 animals revealed no significant difference. Other lung tumors (carcinoma, sarcoma) were rare. They were found in isolated mice who had received isoflurane (3 mice), enflurane (1), and halothane (1). The incidence of exudative pneumonia varied from as little as 5.4% (enflurane females, group 2) to as high as 51.2% (group-1 1/32 MAC halothane male mice).

Kidneys—Abnormalities in the kidneys were infrequent. A single carcinoma was found in a group-1 air control male.

Gonads—There were no instances of abnormal male gonads. The female gonads similarly revealed little pathology except for ovarian cysts, which were found in 20 to 45% of mice. Uterine malignancies were rare. One group-1 N_2O mouse had an endometrial cancer, as did one group-2 methoxyflurane mouse. Two group-1 isoflurane mice (1/8 MAC and 1/32 MAC) had sarcomas, as did two group-2 air control mice. A single hemangioma was found in a group-2 enflurane mouse.

Spleens—The spleens demonstrated little pathology except for lymphomas, which will be described separately.

Livers—The livers evidence two types of neoplastic changes (tables 3 and 4). These were tumors of hepatocyte origin or lesions of the liver vasculature (hemangiomas, hemangioendotheliomas, hemangiosarcomas). The overall incidence of hepatocyte or vascular lesions was 3.1 and 4.4% respectively in male mice. The incidence in female mice was significantly less for both hepatocyte (1.1%) and vascular lesions (2.4%). No significant difference appeared for either lesion between treatments nor was there any association with anesthetic dose.

Lymphomas—Lymphomas were found in the liver, spleen, kidney, uterus, lung, intestine, and thymus of various animals. In a given mouse, often more than one organ was involved. Tables 3 and 4 indicate the incidence of animals afflicted. Intragroup comparisons for the sets in groups 1 and 2 do not show significant differences, with two exceptions: In group 2, male mice given 1/2 MAC isoflurane or halothane had *lower* incidences than the air control set. In addition, the incidence of lymphoma in group-2 isoflurane males (8%) or females (20%) was significantly less than in the combined remaining sets for each sex (22% and 39% respectively). This finding also was reflected in the normal tissue survey (see below).

Other Tumors—For groups 1 and 2, benign or malignant nonlymphomatous neoplasias were found in 27 mice at sites other than lung, liver, spleen, kidney, or gonads (table 5). The 4 mammary tumors listed are of interest. These were all the mammary tumors found. The limited numbers were something of a surprise since this strain of mouse is said to have a high incidence of mammary tumors—19% at 6 months of life.[22]

Incidence of Malignant Changes — We have combined the abnormal tissue data for mice in whom carcinomas or sarcomas (excluding lymphomas) were found at the 15-month harvest with those for animals dying prematurely between 9 and 15 months (table 6). Where an animal had both a carcinoma and a sarcoma, both were listed. However, a sarcoma appearing at multiple sites in a given mouse was listed as a single afflicted animal. The data do not include

TABLE 3
Fifteen-Month Incidence of Liver and Lung Tumors and Lymphomas

			Group 1 (Anesthetic background: O_2)					Group 2 (Anesthetic background: air)				
	Sex	MAC	N	Hepatocyte	Liver vascular lesion	Lymphoma	Pulmonary adenoma	N	Hepatocyte	Liver vascular lesion	Lymphoma	Pulmonary adenoma
Oxygen	M	—	32	3.1(1)	0(0)	12.5(4)	28.2(9)	77	5.2(4)	1.3(1)	24.7(19)	28.6(22)
	F	—	21	0(0)	4.8(1)	23.8(5)	4.8(1)	70	1.4(1)	5.7(4)	34.3(24)	27.1(19)
Air	M	—	53	1.9(1)	1.9(1)	17.1(9)	13.2(7)	58	3.4(2)	8.6(5)	32.8(19)	17.2(10)
	F	—	49	0(0)	0(0)	26.5(13)	14.3(7)	51	0(0)	5.9(3)	39.2(20)	29.5(15)
Isoflurane	M	1/2	58	3.4(2)	0(0)	13.8(8)	18.9(11)	50	2.0(1)	6.0(3)	8.0(4)*	36.0(18)
	F	1/2	57	0(0)	1.8(1)	29.8(17)	21.2(12)	40	2.5(1)	2.5(1)	20.0(8)	25.0(10)
	M	1/8	46	2.2(1)	4.3(2)	2.2(1)	19.5(9)	26	0(0)	11.5(3)	11.5(3)	23.0(6)
	F	1/8	35	0(0)	5.7(2)	20.0(7)	20.0(7)	—	—	—	—	—
	M	1/32	44	4.5(2)	2.3(1)	13.6(6)	15.9(7)	37	5.4(2)	8.1(3)	21.6(8)	13.5(5)
	F	1/32	39	2.6(1)	0(0)	15.4(6)	12.8(5)	—	—	—	—	—
Halothane	M	1/2	55	1.8(1)	3.6(2)	12.7(7)	20.0(11)	62	4.8(3)	6.5(4)	14.5(9)*	37.0(23)
	F	1/2	62	3.2(2)	1.6(1)	17.7(11)	22.6(14)	37	0(0)	2.7(1)	35.1(13)	21.6(8)
	M	1/8	42	2.4(1)	2.4(1)	9.5(4)	21.2(9)	38	2.6(1)	5.3(2)	23.7(9)	15.8(6)
	F	1/8	38	0(0)	0(0)	18.4(7)	10.5(4)	—	—	—	—	—
	M	1/32	41	0(0)	0(0)	12.2(5)	29.3(12)	35	2.9(1)	8.6(3)	14.3(5)	25.8(9)
	F	1/32	27	0(0)	3.7(1)	18.9(7)	37.0(10)					

Enflurane	M	1/2	56	1.8(1)	0(0)	7.1(4)	19.6(11)	37	1.8(1)	7.0(4)	18.9(11)	13.5(11)
	F	1/2	56	0(0)	0(0)	16.1(9)	21.5(12)	37	2.7(1)	5.4(2)	43.2(16)	16.2(6)
	M	1/8	41	4.9(2)	0(0)	22.0(9)	24.4(10)	—	—	—	—	—
	F	1/8	35	2.9(1)	0(0)	25.7(9)	14.3(5)	—	—	—	—	—
	M	1/32	38	2.6(1)	0(0)	18.4(7)	21.0(8)	—	—	—	—	—
	F	1/32	35	0(0)	0(0)	20.0(7)	8.6(3)	—	—	—	—	—
Methoxyflurane	M	1/2	—	—	—	—	—	24	12.5(3)	8.3(2)	29.2(7)	29.2(7)
	F	1/2	—	—	—	—	—	36	0(0)	8.3(3)	44.4(16)	38.9(14)
								Group 3				
N_2O	M	1/2	24	4.2(1)	4.2(1)	4.2(1)	12.5(3)	42	0(0)	4.8(2)	21.4(9)	21.4(9)
	F	1/2	27	7.4(2)	0(0)	37.0(10)	37.0(10)*	33	0(0)	0(0)	33.3(11)	6.1(2)
	M	1/8	33	6.1(2)	6.1(2)	7.0(3)	17.0(7)				—	—
	F	1/8	39	0(0)	0(0)	17.9(7)	15.4(6)	—	—	—	—	—
				Group 4 (Anesthetic background: O_2)								
Methoxyflurane	M	1/2	54	3.7(2)	16.7(9)	7.4(4)	20.4(11)					

For the column indicating lesions, the 1st number is the percentage of animals having the lesion; the number in parentheses indicates the actual number of animals demonstrating that lesion.

*Significantly different from air control

TABLE 4
Combined 15-Month Incidence of Liver and Lung Lesions and Lymphomas for Groups 1 and 2

	Combined male lesions					Combined female lesions				
	N	Hepatocyte	Liver vascular lesion	Lymphoma	Pulmonary adenoma	*N*	Hepatocyte	Liver vascular lesion	Lymphoma	Pulmonary adenoma
Group 1										
O_2	32	3.1(1)	0(0)	12.5(4)	28.2(9)	21	0(0)	4.8(1)	23.8(5)	4.8(1)
Air	53	1.9(1)	1.9(1)	17.1(9)	13.2(7)	49	0(0)	0(0)	26.5(13)	14.3(7)
Isoflurane	148	3.4(5)	2.0(3)	9.5(14)	18.2(27)	131	0.8(1)	2.3(3)	22.9(30)	18.3(24)
Halothane	138	1.4(2)	2.2(3)	12.3(17)	23.2(32)	137	1.5(2)	1.5(2)	18.2(25)	20.4(28)
Enflurane	145	2.8(4)	0(0)	13.1(19)	21.4(31)	126	0.8(1)	0(0)	19.8(25)	15.9(20)
N_2O	63	4.8(3)	3.2(2)	6.4(4)	15.9(10)	66	3.0(2)	0(0)	25.8(17)	24.2(16)
Total	579	2.8(16)	1.6(9)	11.6(67)*	20.0(116)	530	1.1(6)	0.9(6)	21.7(115)	18.1(96)
Group 2										
O_2	77	5.2(4)	1.3(1)	24.7(19)	28.6(22)	70	1.4(1)	5.7(4)	34.3(24)	27.1(19)
Air	58	3.4(2)	8.6(5)	32.8(19)	17.2(10)	51	0(0)	5.9(3)	39.2(20)	29.5(15)
Isoflurane	113	2.7(3)	8.0(9)	13.3(15)	25.7(29)	40	2.5(1)	2.5(1)	20.0(8)	25.0(10)
Halothane	135	3.7(5)	6.7(9)	17.0(23)	28.1(38)	37	0(0)	2.7(1)	35.1(13)	21.6(8)
Enflurane	57	1.8(1)	7.0(4)	19.3(11)	19.3(11)	37	2.7(1)	5.4(2)	43.2(16)	16.2(6)
Methoxyflurane	24	12.5(3)	8.3(2)	29.2(7)	29.2(7)	36	0(0)	8.3(3)	44.4(16)	38.9(14)
Total	464	3.9(18)	6.4(30)†	20.3(94)†	25.2(117)	271	1.1(3)	5.2(14)†	35.8(97)†	26.6(72)

*Significantly different from females

†Significantly different from group 1

For the column indicating lesions, the 1st number is the percentage of animals having the lesion; the number in parentheses indicates the actual number of animals demonstrating that lesion.

TABLE 5
Miscellaneous Tumors Found at 15 Months

Number	Sex	Anesthetic	MAC	Abnormality
Group 1				
1	M	O_2 control		Adipose tissue hemangioma
1	F	O_2 control		Muscle sarcoma
1	M	Air control		Cancer of the stomach
1	F	Air control		Thyroid adenocarcinoma
1	M	Isoflurane	1/2 MAC	Salivary gland adenoma
1	F	Isoflurane	1/8 MAC	Mammary adenocarcinoma
1	F	Isoflurane	1/8 MAC	Adrenal sarcoma
1	F	Isoflurane	1/32 MAC	Mammary adenocarcinoma
1	M	Enflurane	1/2 MAC	Sarcoma—adipose tissue
1	M	Enflurane	1/2 MAC	Mesenteric lymph node carcinoma
1	M	Enflurane	1/2 MAC	Muscle sarcoma
1	F	Enflurane	1/8 MAC	Intestinal adenocarcinoma
1	M	Enflurane	1/8 MAC	Carcinoma—mesenteric lymph node and muscle
1	M	Enflurane	1/32 MAC	Squamous carcinoma—salivary gland
1	F	N_2O	1/2 MAC	Intestinal adenocarcinoma
1	M	N_2O	1/8 MAC	Intestinal adenocarcinoma
Group 2				
1	F	O_2 control		Muscle adenocarcinoma
1	F	O_2 control		Hemangioma of the salivary gland
2	M	Air control		Benign testicular neoplasm (1 hemangioma, 1 benign tumor)
1	F	Isoflurane	1/2 MAC	Colon cancer
2	F	Isoflurane	1/2 MAC	Mammary adenosarcoma
1	M	Isoflurane	1/32 MAC	Adrenal adenocarcinoma
1	M	Isoflurane	1/32 MAC	Skin sarcoma
1	F	Halothane	1/2 MAC	Adenocarcinoma from undetermined site
1	M	Halothane	1/8 MAC	Subcutaneous sarcoma
1	M	Halothane	1/32 MAC	Subcutaneous sarcoma
1	M	Enflurane	1/2 MAC	Benign keratogenic skin tumor

the few cancers or sarcomas fortuitously found in the spleen survey or the normal tissue survey since these surveys applied to selected sets. The abnormal tissue survey revealed that overt malignancies appeared both in control mice and in mice given each of the anesthetic agents. No particular treatment was associated with a significantly higher incidence of malignancies.

Intergroup and Intersex Differences — There were differences in the incidence of hepatocyte and liver vascular lesions, lymphomas, and pulmonary adenomas between the sexes and between the groups. The incidence of liver vascular lesions, lymphomas, and pulmonary adenomas all were significantly higher in group 2 than in group 1 animals. This applied both to male and female mice except for pulmonary adenomas, where the incidence in male mice approached but did not reach the $p<0.05$ level. These differences between groups prevented us from combining control sets in our evalu-

TABLE 6
Summary of Mice Having Carcinoma or Sarcoma

	Males			Females		
	Carcinoma		Sarcoma	Carcinoma		Sarcoma
	N			*N*		
Group 1						
Control						
O_2	32	0.0(0)	0.0(0)	23	0.0(0)	4.3(1)
Air	59	1.7(1)	0.0(0)	64	1.6(1)	0.0(0)
Isoflurane	158	0.6(1)	0.6(1)	151	2.0(3)	2.0(3)
Halothane	155	0.6(1)	1.3(2)	154	0.0(0)	0.6(1)
Enflurane	167	2.4(4)	1.2(2)	152	1.3(2)	0.0(0)
Nitrous oxide	68	1.5(1)	1.5(1)	70	4.3(3)	0.0(0)
Group 2						
Control						
O_2	91	1.1(1)	1.1(1)	85	3.5(3)	0.0(0)
Air	64	0.0(0)	0.0(0)	55	1.8(1)	3.6(2)
Isoflurane	135	3.0(4)	2.2(3)	46	6.5(3)	2.2(1)
Halothane	156	1.9(3)	4.5(7)	42	2.4(1)	0.0(0)
Enflurane	67	0.0(0)	0.0(0)	45	2.2(1)	0.0(0)
Methoxyflurane	29	3.4(1)	0.0(0)	36	2.8(1)	2.8(1)
Group 3	45	0.0(0)	0.0(0)	35	0.0(0)	2.9(1)
N_2O						

N = numbers of animals harvested at 15 months plus animals dying between 9 and 15 months which were autopsied. For the columns indicating carcinoma or sarcoma, the 1st number is the percentage of animals having the lesion; the number in parenthesis indicates the actual number of animals demonstrating that lesion.

ation of treatment effect. Male group-3 mice (N_2O) had a higher incidence of lymphomas than male group-1 mice given 1/2 and 1/8 MAC N_2O. A lower incidence of pulmonary adenomas was found in female group-3 mice than in female group-2 mice. The incidence of lymphomas in group-4 mice (males treated with methoxyflurane) was lower than that in male group-2 mice. Comparison of vascular lesions of the liver in groups 1, 2, and 4 revealed other significant differences. Group 4 mice had a significantly higher incidence of liver vascular tumors than male mice in either groups 1 or 2 or the male O_2 control sets for groups 1 or 2. The higher incidence of liver vascular lesions was not found in group-2 methoxyflurane-treated mice and there was no significant difference between methoxyflurane treated mice in group 2 and the other group 2 treatment or control sets.

Normal Tissue Survey—The survey of normal tissues in group 2 control and 1/2 MAC mice produced one significant result. The incidence of lymphomas in female mice given isoflurane (5%) was less than that found in the sum of the remaining sets (29%). In contrast to the results from examination of abnormal tissues, the incidence of pneumonia or focal inflammatory lesions was low, the highest being 17.5% in the O_2 controls. Isolated neoplastic changes were seen. A sarcoma was found in the liver of an air control animal and a hemangioma was seen in the liver of a mouse that had received methoxyflurane. Zero to 2 animals in each set had pulmonary adenomas. One pulmonary and 1 renal sarcoma was seen in an air control mouse. Two male and 2 female air control mice suffered from splenic sarcoma while 2 enflurane female mice were similarly afflicted. A single hemangioma was found in the uterus of an isoflurane-treated mouse.

All spleens from control and 1/2 MAC treated animals in group 1 were examined

TABLE 7
Spleen Survey, Group 1

	Control				Isoflurane		Enflurane		Halothane		N_2O	
	O_2		Air		1/2 MAC		1/2 MAC		1/2 MAC		1/2 MAC	
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
N	21	32	49	53	56	58	56	65	61	55	26	24
Normal	14.3	40.6	20.4	28.3	21.4	46.6	21.4	30.8	26.2	36.4	23.1	33.3
R.E. hyperplasia	4.8		2.0	1.9		1.7	5.4	7.7	3.3		3.8	4.2
Follicular hyperplasia	38.1	37.5	55.1	47.2	37.5	32.8	44.6	53.8	42.6	38.2	42.3	41.7
Carcinoma				1.9								
Hematopoesis	41.3	12.5	12.2	15.1	12.5	12.1	28.6	7.7	18.0	9.1	23.1	8.3
Focal fibrosia				1.9					1.6			
Lymphoma	33.3	15.6	18.4	18.9	35.7	12.1	17.9	12.3	31.1	20.0	26.9	20.8

Except for "*N*" the numbers indicate the percent of animals displaying the indicated lesion.

microscopically (spleen survey). As in the abnormal survey, only lymphomas and follicular hyperplasia were found in significant numbers (table 7). Isoflurane demonstrated both the highest (females) and lowest (males) incidences of lymphoma. Neither was significantly different from the other treatment or control sets. One male air control suffered from a metastatic carcinoma.

Viral Studies—At the 9-month harvest of group 1 mice, the level of minute virus of mice (MVM) was significant only in the 1/32 MAC halothane treatment set. The 1/2 MAC halothane group had a significant titer of mouse hepatic virus (MHV). No other evidence of previous viral infection was found. At the 15-month sacrifice, group 1 animals in all sets were found to have significant serum levels of Sendai virus antibodies. This is not unexpected.[23] No other serum evidence of viral infection was found in this group. Significant Sendai titers were also found in all sets of group 2. In addition, MVM was found in 2 mice tested in the air controls (1 male and 1 female), 1/2 MAC isoflurane (1 male and 1 female), and the 1/32 MAC isoflurane (2 males) sets. One female O_2 control, and one 1/2 MAC halothane male, and one 1/8 MAC halothane male also had MVM. GDVII was found in a single male in the 1/2 MAC isoflurane set and in the 1/32 MAC isoflurane set.

DISCUSSION

Our results support neither the general thesis that modern inhaled anesthetics are carcinogens nor the earlier suggestion by Corbett that isoflurane is a carcinogen.[10] A few statistically significant results appeared in the large number of comparisons made. However, these significant differences showed no consistent relationship with anesthetic agent or dose. For example, male mice given 1.2 MAC isoflurane or 1/2 MAC halothane in an air background (group 2) had a higher incidence of pulmonary adenomas and lower incidence of lymphomas than their peer air controls (table 3), whereas male mice given the same anesthetics and doses in an O_2 background did not differ from their peer O_2 controls. Group-1 female mice given 1/2 MAC N_2O experienced a higher incidence of pulmonary adenomas than their air control peers.

The viral studies were undertaken to determine whether the incidence of infection from this source could explain any differences in death rates or could be correlated with the appearance of neoplasia. However, the serologic evidence of previous infection was too scattered or too consistent (ie, the appearance of Sendai virus titers in all sets) to explain any differences or support any correlation.

We believe the anesthetic stress we administered was considerable and sufficient to have revealed a potent carcinogen. At the highest dose (1/2 MAC), a total of 28 MAC-hours was given—a dose about 10 to 30 times that experienced by the usual patient. This dose decreased weight gain in our animals. Furthermore, the exposures were given at an age of rapid growth, one supposedly particularly sensitive to the effect of carcinogens.[24]

In many respects our findings confirm those of Corbett. Our tumor incidence usually approached or exceeded that found by

him. For example, our overall incidence of pulmonary adenomas was 21.4%, a figure approaching Corbett's 30% (data by personal communication). Our lymphoma incidence of 20.1% exceeds that which he found (only a few lymphomas were seen), and where we found 4.4% liver vascular lesions in male mice, he found none (a difference which is not significant). Again, our incidence of hepatocyte lesions in females (1.1%) is no different from his (zero). However, in males we found a 3.1% incidence whereas his was 16.7%—a highly significant difference ($p<0.01$).

Why were we unable to confirm Corbett's finding of an increased incidence of hepatocyte lesions in male isoflurane-treated animals? We closely followed the design of Corbett's experiment, deviating only where we believed that design was scientifically unsound. The strain of mouse was identical although the animals came from different vendors. Both vendors trace their original stock back to Roswell Park animals. Our exposure intervals were essentially identical to those used by Corbett and our animals were harvested at the same age.

The doses that we used should have given us a higher incidence of hepatocyte lesions if isoflurane is a carcinogen and its carcinogenic potential is dose related. The highest dose we used (0.6%) was higher by a factor of 2 than Corbett's highest dose. This difference may not be apparent from Corbett's publication, which indicates that he used concentrations which ranged from 0.3 to 0.5%. Furthermore, in Corbett's experiment the isoflurane was not introduced in a square-wave fashion but was delivered at a constant concentration in a 5-L/min flow rate to a 227-L chamber. The low flow rate relative to chamber volume meant that the chamber concentration increased gradually, with a 50% turnover requiring more than a half hour. The 0.3 to 0.5% figure was obtained in the last 45 minutes of each 2-hour exposure and thus overestimates the actual average chamber concentration. The average concentration probably was 0.3% or less. The highest concentration was delivered only during the 4 in utero exposures. For the 25 post-utero exposures, Corbett decreased the inspired concentration to 0.08 to 0.1%. As before, this concentration was measured in the last 45 minutes of exposure and therefore is also an overestimate of the average inspired concentration. Thus, our 1/2 MAC studies exposed the mice to more than 5 times the highest dose-time administration given by Corbett.

Unlike Corbett, we treated our control animals identically to our experimental animals except for the imposition of the anesthetic. Control animals were put in the exposure chamber and were deprived of food and H_2O for the same period as anesthetic-exposed animals. No mice were permitted to eat food which had been exposed to anesthetic.

Perhaps the 4 most important differences between our study and Corbett's were our use of greater numbers of animals, the fact that our animals were raised in California rather than Michigan, the use of controls from peer mothers, and the blind gross and microscopic examination of animals. The potential importance of each of these differences now will be considered.

The greater number of animals per set in our experiment increased the likelihood of discovering a small carcinogenic effect. Similarly, the higher time-dose exposure we used should have increased our chance of uncovering a significant effect.

Mice raised in California as opposed to Michigan may differ in their exposure to many things. Because of the Firemaster disaster, animal food in Michigan was contaminated with polybrominated biphenyls. These compounds are known to be teratogens[25] and their sister compounds, polychlorinated biphenyls, are known to be hepatic carcinogens.[26] We had livers from 7 of our animals and 6 from Corbett's animals analyzed for levels of polybrominated biphenyls (analysis by Anatech Services, Inc., 828 Phoenix Dr., Ann Arbor, Michigan 48104). The levels in our mice were less than the level of detection (0.01 ppm) whereas those from Corbett's animals averaged 0.068 ± 0.014 ppm (mean ± SEM). The results indicate that the Michigan but not California mice were exposed to significant amounts of polybrominated biphenyls and we suggest that this exposure might have contributed to a higher average incidence of liver lesions in Corbett's animals. A possible corollary to this proposition is that the presence of polybrominated biphenyls may heighten the potential carcinogenicity of isoflurane or other anesthetics. The polychlorinated biphenyls are known to induce hepatic microsomes and thereby enhance the metabolism of many compounds, including anesthetics. Perhaps this en-

hanced metabolism is essential to the production of neoplasia. We did not test this possibility. However, biodegradation of the agents used in our study varies from as little as 1% (isoflurane)[18] to as much as 50% (methoxyflurane).[27] Furthermore, repeated administration of anesthetics may produce enzyme induction.[28,29] These facts would not suggest that induction of anesthetic metabolism should be a necessary prerequisite for production of carcinogenicity by anesthetics.

Corbett's male control group (males were the only mice evidencing hepatocyte lesions) actually was two groups. The first (10 mice) was a valid control group in that the mothers were peers of the treated animals. The second (13 mice) was obtained from mothers who were not peers, who had carried their progeny at a different time and in a different building. The importance of this seemingly minor point is indicated by the significant differences in the incidence of tumors among group 1, 2, 3, and 4 animals. This difference precluded our merging the results for the same anesthetic and dose from different groups. If Corbett's results are similarly treated, then he is left with only 10 male control mice, which eliminates any statistical significance from his findings.

The impact of bias on the results from Corbett's study cannot be measured. However, Corbett's thesis was that isoflurane caused cancer. Since he was aware of the treatment imposed on each animal that he examined grossly and microscopically, bias may have influenced the manner in which tissues from anesthetic-treated animals were examined in comparison to controls. The discovery of one hepatocyte lesion in his control set would have eliminated any statistical significance from his results

In conclusion, our results do not support Corbett's earlier suggestion that isoflurane causes hepatocellular neoplasia. Applying his experimental approach, we also find no evidence for the carcinogenicity of enflurane, halothane, methoxyflurane, or N_2O. We cannot say whether a yet more severe stress, longer survival time, or lifetime exposures would uncover some neoplastic potential of specific anesthetics. Similarly, we have not examined the possibility that interactions between anesthetics and other compounds (eg, polybrominated biphenyls) might lead to cancer. Nonetheless, our results and the recent results of other animal and human studies* suggest that the risk of malignancy due to anesthetic exposure is at most very small and possibly nonexistent.

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*Unpublished data presented at the 1977 American Society of Anesthesiologists meeting by RI Mazze, JM Baden, RS Wharton, et al (animal data) and by N Greene and P Cohen (human data).

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Respiratory Function Following Premedication with Droperidol or Diazepam

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Respiratory function was measured before and 1 hour after premedication with diazepam (10 mg IM) or droperidol (5 mg IM) in 2 groups of 14 normal patients scheduled for elective surgery. Diazepam had no significant effects on respiratory rate, tidal volume, minute ventilation, dead space, VD/VT %, alveolar ventilation, expired P_{O_2}, or P_{CO_2}, end-tidal P_{CO_2}, arterial P_{O_2} or P_{CO_2}, or alveolar-arterial P_{O_2} or P_{CO_2} gradients. Droperidol was associated with statistically significant but modest reductions in tidal volume (−13.3%) and minute ventilation (−8.4%) while other respiratory functions remained unaffected.

Key Words—HYPNOTICS, benzodiazepines, diazepam. ANESTHETICS, intravenous, droperidol. VENTILATION, diazepam. VENTILATION, droperidol.

THE criteria for selecting a drug as a preoperative sedative are based upon achievement of maximal sedation with minimal hemodynamic and respiratory effects. While narcotic drugs have been used for this purpose, in recent years more attention has been focused on the use of tranquilizers such as droperidol and diazepam.[1-3] Diazepam when administered alone in a dose of 10 mg IM has been reported as being free of respiratory depression but contradictory reports about its effects on airway resistance have been published.[4,5] The few reports which have been published about the respiratory effects of droperidol when administered alone[3-7] suggest that droperidol may be free of respiratory depression when administered in the doses clinically used during premedication, but the data are inadequate to prove the nature and magnitude of potential ventilatory responses to premedicant doses of droperidol.

We compared the effects of droperidol and diazepam on respiratory function when administered in doses that are commonly regarded as equieffective as premedicants for the relief of anxiety and apprehension.

METHODS AND MATERIALS

Twenty-eight ASA category I or II patients of both sexes aged 20 to 50 years with normal pulmonary function were selected from patients scheduled for elective general surgical procedures. Patients were told about the nature of the study. Written consent was obtained.

The following pulmonary-function tests were performed (only patients with normal

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results were included in the study): Lung volumes were determined by using the Godart pulmonet. The best of 3 successive values was selected and converted to body temperature and pressure saturated with water vapor (BTPS). Measured volumes were expressed as a percentage of the predicted values. Normal values were as reported by Needham et al.[8] Functional residual capacity (FRC) was measured by the helium dilution method, normal values being considered those reported by Menneely and Kaltreider.[9] Mechanics of breathing were measured by using a pneumotachograph for forced expiratory volume in 1 second (FEV_1) and by using a variable pressure body plethysmograph for measurement of airway resistance (R_{aw}) and thoracic gas volume (V_{tg}). Airway conductance was expressed as the reciprocal of airway resistance. An FEV_1 more than 85% of the vital capacity was considered normal. The values for airway resistance reported by Du Bois et al[10] were considered normal for our subjects.

Arterial oxygen (Pao_2) and carbon dioxide ($Paco_2$) partial pressures were measured using a Radiometer Blood Gas Analyzer. Samples of arterial blood were obtained through a percutaneous plastic cannula inserted into the dorsalis pedis artery using a heparinized syringe without air contamination. Samples were immediately placed in ice and analyzed within 30 minutes. Patients breathed room air and rested at least one-half hour before withdrawal of the sample.

Expired CO_2 partial pressure ($P_{\bar{E}}co_2$) was measured using a Douglas bag in which 3 minutes of expired air was collected and analyzed using a Radiometer Blood Gas Analyzer. Patients were resting at least one-half hour before the test while breathing room air. Expired O_2 partial pressure ($P_{\bar{E}}o_2$) was measured by using the same method as was used for expired $P_{\bar{E}}co_2$.

End-tidal CO_2 partial pressure ($PETco_2$) was measured using a Godart Capnograph with results converted to $PETco_2$ after correction for atmospheric pressure and water vapor pressure saturation.

Patients were numbered from 1 to 28 according to their order of entry into the study. The drugs were administered by random selection. Neither the patient nor the anesthesiologist who performed the measurements was aware which drug had been administered. Patients fasted for at least 6 hours before the initial measurements were taken. None of the patients received any medication for at least 4 weeks before the study. No medication was administered the evening before the operation.

The study was performed during the morning of scheduled surgery. Using the technics described above, the following variables were measured prior to and 1 hour after administration of diazepam (10 mg IM) or droperidol (5 mg IM): respiratory rate (RR); tidal volume (VT); minute ventilation (converted to body temperature and pressure saturated with water vapor $V_{\bar{E}}BTPS$); dead space (VD), calculated using the Bohr equation

$$VD = VT\frac{Paco_2 - P_{\bar{E}}co_2}{Paco_2} - VD\ valve$$

where VD valve is the dead space of the valve used in the Douglas bag (in our case 16 ml); VD/VT%; alveolar ventilation, calculated by subtracting the VD from $V_{\bar{E}}BTPS$; $P_{\bar{E}}o_2$; $P_{\bar{E}}co_2$; Pao_2; $PETco_2$; $Paco_2$; and alveolar-arterial O_2 partial pressure (A-a DO_2) and alveolar-arterial CO_2 partial pressure differences (A-a Dco_2), alveolar Po_2 and Pco_2 being calculated from the formula for ideal alveolar gas.[10]

RESULTS

Table 1 summarizes the results obtained in patients receiving diazepam. Mean values and standard errors obtained prior to and 1 hour after diazepam are shown, as well as mean values and standard error of the differences before-minus-after treatment for each variable. A *t*-test for paired samples was made for each one of the studied variables and its results are also shown in table 1. We accepted as significant p levels below 0.05. No statistically significant changes were observed in any of the variables studied.

Table 2 summarizes the results obtained in patients given droperidol. A statistically significant mean reduction in tidal volume of 75.6 ml (−13.3%) occurred. There was also a significant mean reduction of 800 ml/min (−8.4%) in minute ventilation converted at standard temperature and pressure of dry gas ($V_{\bar{E}}STPD$). The same significant mean reduction of 800 ml/min (−7.0%) occurred in minute ventilation corrected at body temperature and water vapor pressure saturation ($V_{\bar{E}}BTPS$). A significant mean reduction in dead space

TABLE 1

Respiratory Function in Patients Before and One Hour After Diazepam

	Before			After			Differences			
	Mean	n	SE	Mean	n	SE	Mean	n	SE	t*
RR	20.6	14	1.57	22.3	14	1.77	−1.7	14	1.00	−1.7
V_T (ml)	669.2	14	50.88	596.1	14	50.91	73.1	14	40.43	1.8
V_EBTPS (lts/min)	13.7	14	1.60	12.9	14	1.51	0.8	14	0.78	1.03
V_ESTPD (lts/min)	11.3	14	1.33	10.6	14	1.27	0.7	14	0.65	1.08
V_D (ml)	269.1	14	29.27	222.6	14	24.09	46.5	14	21.56	2.16
V_D/V_T (%)	38.7	14	1.47	34.7	14	1.95	4	14	2.38	1.68
Alv. vent. (ml/min)	8254.9	14	720.98	8534.7	14	1102.49	−279.8	14	777.33	−0.36
P_EO_2 (mm Hg)	129.3	14	0.99	129.9	14	1.01	−0.6	14	0.96	−0.62
P_ECO_2 (mm Hg)	16.0	14	0.32	17.4	14	0.77	−1.4	14	0.69	−2.03
PET CO_2 (mm Hg)	34.3	14	0.89	33.9	14	1.02	0.4	14	0.56	0.74
Pa_{O_2} (mm Hg)	102.4	14	2.44	105.7	14	2.03	−3.3	14	2.78	1.19
Pa_{CO_2} (mm Hg)	34.3	14	0.47	33.8	14	0.74	0.5	14	1.07	0.47
(A-a)D_{O_2} (mm Hg)	7.0	14	2.79	5.6	14	2.20	1.4	14	3.05	0.46
(A-a) D_{CO_2} (mm Hg)	−0.31	14	1.055	−0.04	14	1.038	−0.27	14	1.392	0.19

*t for paired samples

See text for abbreviations.

also was observed, but since calculation of dead space is made by using tidal volume, no biologic significance is attributed to that change. None of the other variables changed significantly.

Comparison between initial values for both groups shows a significant difference for VT, V_EBTPS, V_ESTPD, VD, and alveolar ventilation (t-test for unpaired samples; $p<0.05$) with consistently higher values in patients premedicated with diazepam. This difference between groups is interpreted as due to differences in body surface areas that were not taken into consideration in calculation of the studied variables; this difference does not invalidate our results since statistical comparisons were made within groups, not between groups.

DISCUSSION

Our results confirm previous reports that similar doses of diazepam do not produce significant respiratory depression.[1,2] A limited number of studies of the respiratory effects of droperidol when used alone in human clinic have been published. In doses similar to those used by us, droperidol has been found to produce significant reduction in total body O_2 consumption while respiratory and ventilatory parameters remain unchanged.[3] We found a significant but modest reduction in tidal volume and minute ventilation with no significant changes in respiratory rate, blood gas tensions, or other respiratory parameters. The reduction in tidal volume was secondary to reduction in lung expansion during inspiration; reduction of minute ventilation was secondary to the reduction in tidal volume since respiratory rate was not reduced after administration of the drug. Blood gas tensions remained unchanged because the reduction in tidal volume was so slight it had no discernible effect on gas exchange.

The reduction in tidal volume associated with droperidol could be the result of (a) relief of anxiety, (b) extrapyramidal dyskinesia of respiratory muscles induced by the drug, or (c) respiratory-center depression.

TABLE 2
Respiratory Function in Patients Before and One Hour After Droperidol

	Before			After			Differences			
	Mean	n	SE	Mean	n	SE	Mean	n	SE	t*
R R	21.1	14	1.15	22.4	14	1.45	−1.3	14	0.97	−1.34
V_T (ml)	566.8	14	42.23	491.2	14	36.81	75.6	14	20.43	3.70†
$V_{\bar{E}}$BTPS (lts/min)	11.4	14	0.48	10.6	14	0.51	0.8	14	0.27	2.96†
$V_{\bar{E}}$STPD (lts/min)	9.5	14	0.46	8.7	14	0.45	0.8	14	0.23	3.48†
V_D (ml)	212.9	14	25.25	162.4	14	17.39	50.5	14	20.16	2.50†
V_D/V_T (%)	36.9	14	1.79	33.9	14	2.44	3.0	14	2.49	1.20
Alv. vent. (ml/min)	7108.8	14	255.84	7046.9	14	387.63	61.9	14	342.35	0.18
$P_{\bar{E}}O_2$ (mm Hg)	130.1	14	0.96	129.9	14	0.96	0.2	14	0.95	0.21
$P_{\bar{E}}CO_2$ (mm Hg)	16.1	14	0.51	17.3	14	0.79	−1.2	14	0.62	1.93
PET CO_2 (mm Hg)	34.5	14	0.94	33.3	14	1.13	1.2	14	0.63	1.90
Pa_{O_2} (mm Hg)	104.6	14	3.02	108.9	14	2.18	−4.3	14	2.43	1.77
Pa_{CO_2} (mm Hg)	34.4	14	0.74	33.5	14	0.85	0.9	14	0.61	1.47
(A-a) D_{O_2} (mm Hg)	4.3	14	3.43	2.6	14	1.61	1.7	14	1.00	1.70
(A-a) D_{CO_2} (mm Hg)	−0.4	14	1.01	−0.2	14	1.25	−0.2	14	1.17	−0.17

*t for paired samples

†$p<0.05$

See text for abbreviations.

Droperidol is a neuroleptic drug of the butyrophenone type which produces in the majority of patients an indifference to one's surroundings with mental detachment. In a minority of cases, however, agitation, fear, anxiety, or refusal to undergo surgery previously agreed to may be produced.[14] By relieving apprehension and anxiety, the drug may produce a more basal respiratory state with a slight reduction in tidal volume but without significant hypoventilation, as observed in this study. However, we did not observe a similar response in patients premedicated with diazepam, which we would expect if the antianxiety potency of the drugs is equivalent in the doses administered. Comparisons between drugs in terms of their ability to relieve something as subjective as anxiety are notoriously difficult; equivalent doses for diazepam and droperidol have not been established. Morrison et al[3] compared droperidol 5 mg and 10 mg IM with diazepam 10 mg IM as premedicants, and found that 5 mg droperidol and 10 mg diazepam were similar in their ability to relieve apprehension. However, droperidol, while producing less drowsiness, was associated with greater restlessness than was diazepam. Our clinical experience agrees with that of Morrison et al: the most effective doses for the relief of anxiety and fear are droperidol 5 mg and diazepam 10 mg, and these represent clinically equieffective doses. Although droperidol reaches its maximal plasmatic levels faster than diazepam does when administered by IM route, peak antianxiety effects are reached 1 hour after administration of both drugs,[3] the period we used in our study. Thus, we studied approximately equally effective doses of the 2 drugs at equally effective times.

Droperidol is capable of producing extrapyramidal side effects, including extrapyramidal dyskinesia of voluntary muscles.[6] Rigidity of thoracic muscles with impairment of respiration has also been described when droperidol is administered with fentanyl for neuroleptoanalgesia. Extrapyramidal dyskinesia of respiratory muscles may hinder in-

spiration and thus reduce tidal volume and minute ventilation. Diazepam does not have this side effect and so would not be expected to be associated with changes in respiratory function. We suggest that the extrapyramidal dyskinesia of respiratory muscles associated with droperidol may be responsible for the decrease in tidal volume which it causes.

We do not believe in depression of respiratory center as the possible cause for the observed effects of premedication with droperidol since others have found that the dose of droperidol we used, 5 mg, has no significant effects on ventilation in man.[3-7]

In conclusion, we believe that observed reductions in tidal volume and minute ventilation after premedication with droperidol are more likely due to extrapyramidal dyskinesia of respiratory muscles produced by the drug, although the antianxiety effect of the drug or respiratory center depression cannot be ruled out as possible causes. Diazepam tested at doses with similar antianxiety potency did not produce significant changes in respiratory function.

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Domperidone in the Treatment of Postoperative Vomiting: A Double-Blind Multicenter Study

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Domperidone was compared with placebo in a multicenter double-blind study of 116 patients (15 to 80 years) with postoperative vomiting. After vomiting had occurred, the patients received either domperidone 10 mg or placebo IV. Patients were then followed for at least 6 hours or until a 2nd injection of domperidone 10 mg from an open supply was needed. The period of time until an additional injection was registered and compared between the 2 treatment groups. Fifty-nine percent of the placebo patients needed a 2nd injection before the end of the 6-hour follow-up, compared with only 35% of the domperidone patients ($p<0.05$). When a 2nd injection was required, the time elapsed before it was needed was longer ($p = 0.01$) in the domperidone group (median 150 minutes) than in the placebo one (median 120 minutes). There were no significant side-effects.

Key Words — VOMITING, antiemetics, domperidone.

NAUSEA and vomiting are among the most troublesome postoperative problems. Since they may undermine the patient's condition, a safe and efficient remedy would be welcome.

Such a remedy would be expected to antagonize the emetic effects of both anesthetics and potent analgesics, and to alleviate gastrointestinal atonia, which may contribute to nausea and vomiting. Some drugs which are effective in controlling nausea and vomiting, however, produce untoward effects such as sedation, extrapyramidal symptoms, and hypotension, whereas others lack sufficient effectiveness.

The new synthetic substance domperidone (R 33 812, fig 1) has potent antiemetic as well as gastrointestinal stimulatory properties[7,9] though, chemically, it does not belong to one of the well-known classes of antiemetics. Pharmacological experiments have shown[6,11] that domperidone is a peripheral

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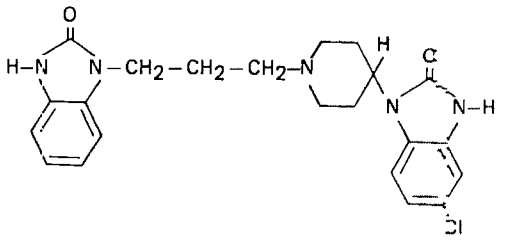


FIG 1. Structural formula of domperidone (R 33 812)

dopamine-blocker.[1] It antagonizes apomorphine-induced vomiting in dogs, but it has no effect on the central nervous system. Both after oral and parenteral IV or IM administration it is rapidly distributed in the tissues and metabolized in the liver; fecal excretion of metabolites is the main route of elimination. Domperidone has an unusually wide safety margin in toxicity tests.[5]

Clinical studies have confirmed the antiemetic properties of domperidone in peciatric practice,[1,2] in vomiting induced by cytostatic therapy in adults,[3,4,8] and in postoperative vomiting.[10] In postoperative patients, 4 mg of domperidone provided protection in most instances for at least 4 hours. Our double-blind placebo-controlled study was designed to determine whether a higher dose of domperidone might produce a superior antiemetic effect.

MATERIAL AND METHODS

To reduce personal bias, the trial was carried out in 6 practices, comprising 8 doctors. Altogether 116 patients who had already vomited during their postoperative recovery phase were selected for this study. Their main characteristics are given in table 1.

Nausea and vomiting were defined as follows. Nausea was an unpleasant sensation that vomiting might occur. Vomiting was the forcible ejection of gastric contents. Retching was not classified as vomiting, it being a nonproductive expulsive effort.

TABLE 1
Patient Characteristics

		Domperidone group ($n = 58$)	Placebo group ($n = 58$)	Total population ($n = 116$)
Sex:	males	16	10	26
	females	42	48	90
Age:	median (yrs)	41	41	41
	range	15-80	18-80	15-80
Weight:	median (kg)	65	69	67
	range	45-82	50-97	45-97

After vomiting had occurred, the patients were treated with either 10 mg domperidone or placebo. The type of treatment was determined by randomization and the treatment itself was double-blind. Each patient was observed following injection to determine if nausea and/or vomiting continued to be troublesome enough to necessitate further antiemetic therapy (i.e., 10 mg domperidone from an open supply). The patients were followed until they had received this open injection, or, if they did not need it, for at least 6 hours. The time at which a 2nd, open, injection was given was recorded as was the reason for its administration.

Side-effects were noted.

For the statistical evaluation of the findings, the time from the injection of the double-blind medication until the need for "open" treatment was calculated for each patient; these durations were then compared between the 2 treatment groups (domperidone and placebo) by means of the Mann-Whitney U-test. Also, the differences between the number of patients in both groups actually receiving the "open" injection were evaluated, using the chi-square test.

RESULTS

The randomization resulted in 2 groups which were comparable insofar as patient characteristics (table 1), types of operations, and anesthetics (table 2) were concerned.

Three patients, all belong to the domperidone group, were excluded from the analysis. Reasons for this exclusion were violations of the protocol: 2 patients received a 2nd injection of (open) domperidone before nausea or vomiting had recurred; the 3rd received a neurolept with antiemetic properties (haloperidol).

Fifty-nine percent of the placebo-treated patients needed a 2nd (domperidone) injection before the end of the observation period, compared with only 35% of the domperidone patients (table 3 and fig 2). This difference is statistically significant ($p<0.05$). After the double-blind injection, the time elapsed until an additional injection was required was significantly longer ($p = 0.01$) in the domperidone group (median 150 minutes) than in the control population (median 120 minutes). This difference is fur-

TABLE 2
Operation and Anesthesia

	Domperidone group ($n = 58$)	Placebo group ($n = 58$)
Duration of operation (hours)*	1.00 (0.17-7.00)	1.39 (0.17-3.50)
Type of operation†:		
abdominal	22	21‡
other	36	38‡
Premedication†:		
atropine	31	32
droperidol + fentanyl	13	12
diazepam	12	10
other	21	27
Anesthetics†:		
narcotics	52	51
gases: total	48	46
N_2O	42	45
halothane	13	6
hypnotics	44	43
neuroleptics	24	29
other: pancuronium	20	11
succinylcholine	12	13
neostigmine	9	10
atropine	8	10

*Median value (range)
†Number of patients
‡One patient had both an abdominal and a vaginal operation.

ther illustrated by the fact that half of the patients given placebo had already received a supplementary injection after 4 hours, whereas more than half of the patients given domperidone still did well without a 2nd injection after 6 hours.

The only side-effects found in this study were facial flushing, immediately after the double-blind injection (1 domperidone patient), somnolence (1 placebo patient) and hypotension with dyspnea (1 placebo patient); in the latter 2 cases there was no evident relationship to administration of the double-blind medication. There were no extrapyramidal side-effects or excessive sedation after the use of domperidone.

DISCUSSION

The results reported here are in line with those of a previous double-blind placebo-controlled study in which 4 mg domperidone were used.[10]

Our results, using 10 mg of domperidone, do not appear better if one considers the proportion of patients protected by the in-

TABLE 3
Time Until Supplementary Domperidone Injection

Study group	No. patients having received injection within stated time											
	3-60 min*	1-1½ hrs	1½-2 hrs	2-2½ hrs	2½-3 hrs	3-3½ hrs	3½-4 hrs	4-4½ hrs	4½-5 hrs	5-5½ hrs	5½-6 hrs	No injection before 6 hrs
Domperidone No.	1	6	1	4	1	5	0	0	1	1	0	35
cumulative % ($n = 55$)	1.8	12.7	14.5	21.8	23.6	32.7	32.7	32.7	34.5	36.4	36.4	...
Placebo No.	1	9	9	4	3	1	3	2	1	0	1	24
cumulative % ($n = 58$)	1.7	17.2	32.8	39.7	44.8	46.6	51.7	55.2	56.9	56.9	58.6	...

*Injections of antiemetic agents were prohibited by the protocol during the 1st hour.

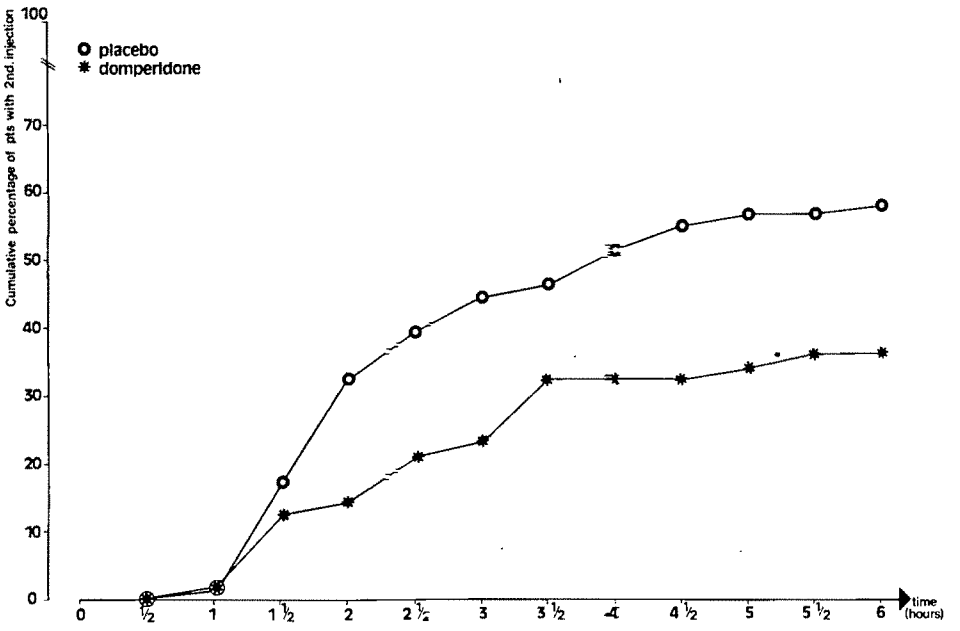


FIG 2. Time until supplementary injection of domperidone

jection. However, the patients in the 4-mg study were followed up for 4 hours only and we found a substantial protection with 10 mg for at least 6 hours. Therefore, it appears possible, though not proven, that the administration of the higher 10-mg dose results in a more protracted effect.

Our data clearly confirm that in the treatment of postoperative nausea domperidone is a potent remedy, virtually devoid of side-effects, in contradistinction to other antiemetics such as prochlorperazine and benzquinamide.

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Review Article

Pharmacokinetics of Drugs Administered Intravenously

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PHARMACOKINETICS is the quantitative study of drug disposition in the body. It includes processes of *absorption* from sites of administration, *distribution* to body tissues and fluids, *biotransformation* to pharmacologically active and inactive metabolites, and *excretion* of the drug and its metabolites from the body. An understanding of the uptake and distribution of inhalational anesthetics is the basis for their safe and effective use. In the same way, information about the pharmacokinetics of IV anesthetics and adjuvant drugs is essential for their efficient use, and even offers the potential for control of the intensity of their effects, an advantage no longer exclusively held by inhalational anesthetics.

What information about drug disposition and pharmacokinetics is useful to the practicing anesthesiologist? How are graphic plots of drug concentration vs time interpreted? What are the limitations of pharmacokinetics? This review is an attempt to answer these questions in order to aid the reader in the interpretation of pharmacokinetic studies.

The reader should note that only a minimum number of mathematical expressions is included in this review. It is hoped that these will not dissuade him from continuing his study of the subject. Extensively detailed treatises laden with mathematics are available,[1,2] as are reviews at an intermediate level.[3]

RATIONAL BASIS OF DRUG DISPOSITION STUDIES

It is generally true that there is a direct relationship between the dose and the resulting concentration of a drug at its site of action and the intensity of its actions. Certainly for a drug reacting reversibly with its receptors, the drug concentration at its site of action determines the intensity of its effect. This relationship can be represented by the reaction:

$$\text{Drug} + \text{Receptor} \rightleftharpoons \text{Drug-receptor complex} \rightarrow \text{Effect}$$

Under ordinary circumstances of acute drug therapy the number of available receptors is constant, and the formation of the drug-receptor complex is dependent only on the concentration of the drug; that is, it follows first-order kinetics (see below). It is also true that for this type of drug-receptor reaction the onset and duration of drug effects will be related to the rise and fall of the drug concentration at its site of action. Seldom can the investigator directly determine the concentration of a drug at its site of action. Instead, he analyzes tissues and fluids that are likely to approximate the site of action in terms of their drug concentration. In human and whole animal experiments, the most readily available specimen likely to correspond to sites of action in regard to the rise and fall of drug concentration is plasma.

As indicated in fig 1, the concentration of drug (D) in plasma plays a central role in the disposition of the drug throughout the body. Drug is absorbed into plasma from enteral and parenteral sites of administration, or is placed directly into plasma by IV injection. Plasma in the circulating blood delivers the drug to sites of action, storage, biotransformation, and excretion. Metabolites formed by biotransformation of the drug may also enter plasma and be distributed throughout the body. Because plasma is the medium in which drug is delivered

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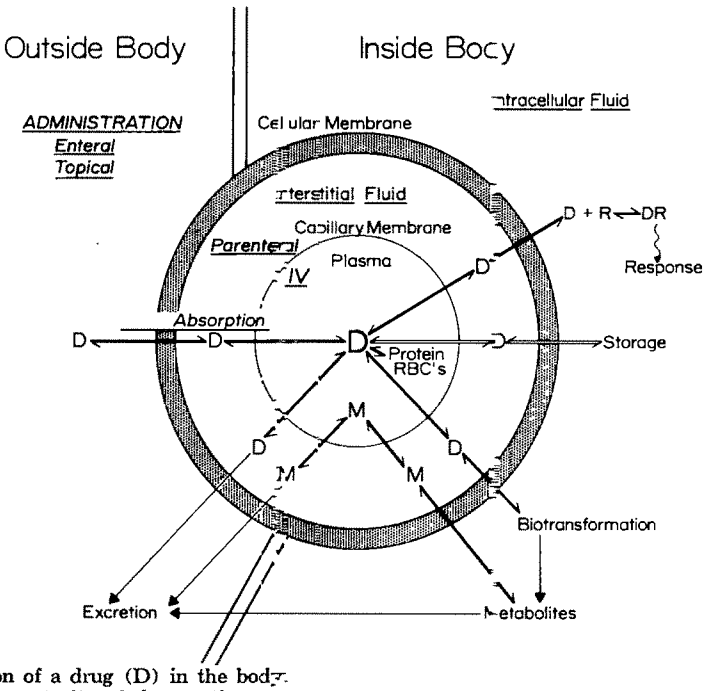


FIG 1. Disposition of a drug (D) in the body.
R—receptor at site of drug action.
M—metabolite(s) of drug, which can enter same disposition processes shown for D.
*Note that one-way arrows are used for biotransformation and excretion since these processes are nonreversible.

and removed from its sites of action, the concentration of drug at these sites should be *proportional* (not necessarily equal; see below) to its concentration in plasma. Moreover, factors affecting the concentration of the drug in plasma will also affect its concentration at sites of action. Thus, removal of the drug from plasma by tissues that store, metabolize, or excrete it ultimately leads to a lower concentration of drug at its site of action.

A basic premise of pharmacokinetic studies is that by measuring concentrations in plasma it is possible to estimate its concentration at sites of action, or at least to follow the rise and fall of drug concentration at sites of action. Such information can be useful in the description of the onset and duration of drug effects; in the identification of factors (eg, disease, interactions with other drugs) that may alter the onset, intensity, and duration of drug action; and in the prediction of the consequences of using different dosing regimens (ie, dose size and frequency of administration).

DETERMINANTS OF DRUG CONCENTRATION IN PLASMA

Three primary factors determine the concentration of drug in plasma: (1) mode of drug administration, (2) uptake of drug by body tissues, and (3) elimination of drug from the body.

Mode of Drug Administration

In the case of intravenously administered drugs, the drug is introduced directly into plasma and there is no delay due to absorption processes. Plasma levels depend on the dose size and its rate of injection. With single bolus doses, the rate of entry is almost instantaneous and the maximum concentration is present immediately after completion of the injection. Thereafter, the concentration of drug in plasma declines progressively unless additional doses are administered intermittently or a continuous infusion is begun. The progressive decline of plasma levels after a single IV dose occurs because the drug enters body tissues and organs. Notice in fig 1 that the drug must penetrate capillary and, in many cases, cellular membranes to gain access to sites of action, storage, biotransformation, and excretion. Thus, a major determinant of the rate of drug exit from plasma is the rate at which the drug penetrates biological membranes.

Drug Equilibration Across Biological Membranes — Biological membranes offer

several routes of penetration: (1) diffusion through aqueous filled channels or pores, (2) dissolution and diffusion in the lipoprotein matrix, and (3) specialized processes such as carrier-mediated transport and pinocytosis. The availability of these different routes of penetration to a drug varies with the type of membrane and with the physicochemical properties of the drug molecule. For example, the size and number of pores is greater in the membranes of vascular capillaries than in cellular membranes found in most tissues. Specialized transport mechanisms for drugs are likewise limited to certain organs and quite specific for the chemical configuration of the compounds they will accept for transport. By far, most drugs penetrate most membranes by dissolution and diffusion in the lipoprotein matrix of the membrane.

The physicochemical properties of drugs that influence their rate of diffusion across membranes are lipid solubility, ionization, and molecular size.

Lipid Solubility—This is the most important property. The greater the lipid solubility (usually expressed as the drug's partition coefficient between an organic solvent and an aqueous buffer), the more rapidly the drug penetrates all types of membranes.

Ionization—Ionization of a drug limits its rate of penetration because ionization both reduces its lipid solubility and causes it to be repelled from similarly charged portions of a membrane or attracted and bound by oppositely charged membrane components. Ionization greatly affects the rate of penetration of parenchymal cellular membranes by most drugs but has little or no effect on their diffusion across vascular capillaries.

Ionization is complete for certain drugs (eg, muscle relaxants with a quaternary nitrogen) and is partial for weak acids and bases with a pKa* close to the range of pH values found in physiologic fluids. If the unionized form of the drug (a weak acid or base) readily penetrates membranes and the ionized form does not, a concentration gradient can occur across membranes separating fluids of different pH (fig 2). At equilibrium the concentrations of unionized drug are the same on both sides of the membranes, but the *total* amount of drug may be considerably different. This is an important consideration in pharmacokinetics since (1) one form of the drug may be more active pharmacologically than the other, and (2) plasma and tissue levels of total drug may differ

*pKa is the pH at which half of a drug exists in its ionized form, half in its unionized form.

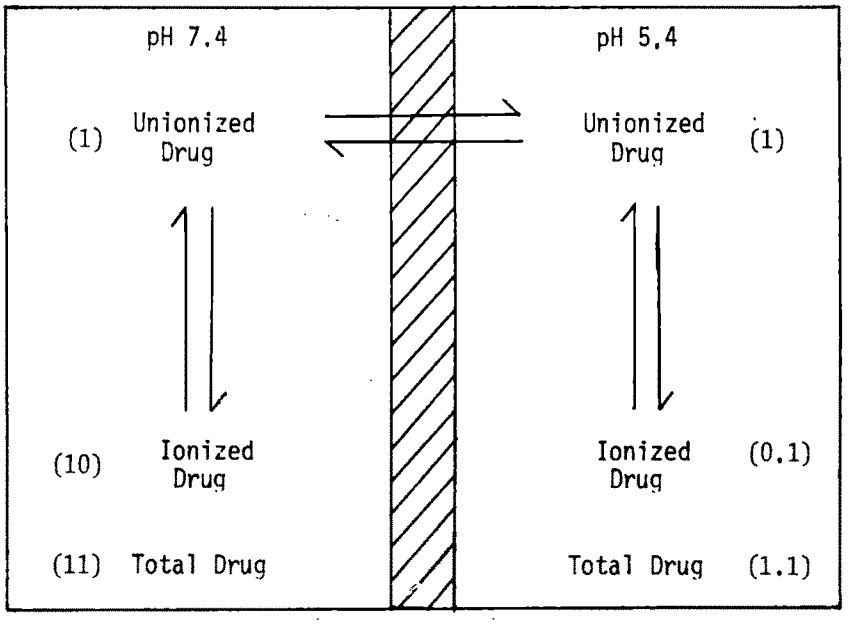


FIG 2. A drug with a pKa of 6.4 is partially ionized as a weak acid ($RH \rightleftharpoons R^- + H^+$) in aqueous fluids separated by a membrane permeable only to the unionized form of the drug. At steady state the total quantity of drug is 10 times greater in one fluid than in the other while the concentration of unionized drug is the same.

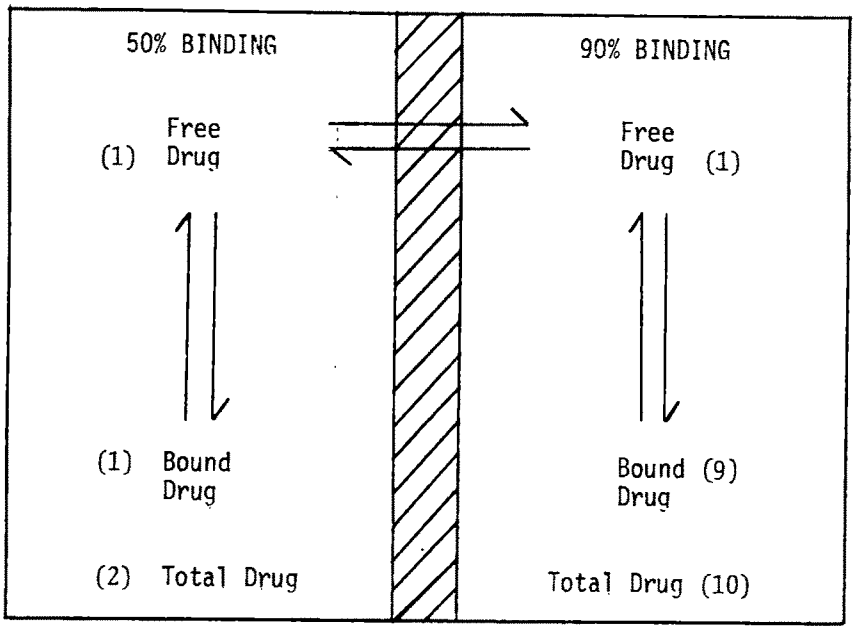


FIG 3. A membrane permeable only to the free form of the drug separates fluids in which the degree of binding of the drug to macromolecules differs. At steady state the total amount of drug is 5 times greater in one fluid than in the other, while the concentration of free drug is the same.

on this basis. Analytical technics measure total drug concentration and do not distinguish between ionized and unionized forms.

Molecular Size—Molecular size is a feature of considerable importance in terms of penetration of membranes by way of pores. Most drugs administered by anesthesiologists have a molecular size too large for penetration of pores in membranes of parenchymal cells. On the other hand, their molecular sizes are sufficiently small to permit their penetration of pores in vascular capillary membranes.

Capillary membranes markedly restrict the penetration of large molecules such as proteins. Almost all drugs are bound to some degree by plasma proteins, especially albumin, and the bound drug does not participate directly in the equilibration of the drug concentrations across membranes (fig 3). Rather, it is only the unbound, free drug that has the same concentration on both sides of a membrane at equilibrium. Thus, if a drug is bound to nondiffusible substances on one side of a membrane and not on the other, the *total* amount of drug will be greater on the side where it is bound. An understanding of the significance of protein binding is of great importance in pharmacokinetics, because most technics for analysis of drugs in plasma measure total drug (ie, both free and protein-bound), while it is only the free drug that is pharmacologically active and equilibrates between plasma and tissues.

From the above discussion it is evident that both the physicochemical properties of the drug as well as characteristics of the particular type of membrane it faces influence its rate of entry into tissues. All of these factors taken together determine the permeability coefficient for the particular drug and a particular membrane. The permeability coefficient is one of several major factors that determine the rate of uptake of a drug by body tissues and organs.

Uptake of Drug by Body Tissues

The uptake of drugs by tissues can be characterized in terms of *rate* and *capacity* (table 1). Blood flow determines the rate of delivery of the drug to (and removal from) tissues. For drugs able to penetrate membranes rapidly, tissue perfusion can be the rate-limiting factor in the exchange of drug between plasma and tissues. The concentration gradient of the diffusible form(s) of the drug determines both the rate and the direction of net transfer between plasma and the tissue. Immediately after an IV injection, when the plasma concentration of the drug is the highest, the entry of the drug into tissues is most rapid. As soon as some of the drug enters tissue, the concentration

TABLE 1
Rate and Capacity of Tissue Uptake of Drugs

Rate of tissue uptake of drug is determined by:
Blood flow
Concentration gradient of diffusable form of drug
Permeability coefficient of drug
Membrane characteristics
Capillary
Cellular
Physicochemical properties of the drug
Lipid solubility
Ionization
Molecular size
Protein binding
Special features
Blood-brain barrier
Membrane transport mechanisms
Metabolism of drug in tissue
Maternal-placental-fetal relationships
Capacity of tissue to take up drug is determined by:
Tissue/plasma partition coefficient
Dissolution in lipids
Binding to macromolecules
pH-dependent partitioning
Active transport
Mass of tissue
Nonreversible processes removing drug from equilibrium
Covalent binding
Metabolism
Excretion

gradient is reduced and the rate of entry slows. As the concentration builds up in tissue and continues to fall in plasma (because the drug is being taken up by tissues and also eliminated from the body), a point will be reached at which the concentrations in plasma and tissue are equal. At equilibrium the gradient is zero and the net exchange of the drug is also zero. With continuing elimination of the drug from plasma, the gradient will then be reversed and the net exchange of drug will be from tissue to plasma. Thereafter, the concentration of drug will decline in both plasma and tissue.

Other factors determine the *capacity* of a tissue to take up a drug (table 1). The tissue/plasma partition coefficient represents the affinity of the tissue for the drug and can be estimated by dividing the drug concentration in the tissue by that in plasma at a steady state (ie, no net transfer of drug between plasma and tissue). The magnitude of the partition coefficient does *not* indicate the *basis* of a greater or lesser affinity of the tissue for the drug. A drug may be highly concentrated in a tissue by active transport into cells, by binding to tissue components, by dissolution in lipids, and by pH-dependent partitioning (fig 2). It is important to note that capacity is a function of both the partition coefficient of the drug and the mass of the tissue. Thus, skeletal muscle may have only a moderate affinity for a drug compared to other tissues, but it nevertheless assumes a dominant role in the disposition of most drugs because of its large mass (approximately 50% of body weight).

The accumulation of a drug in a tissue, even in a tissue with great affinity for the drug, can be limited by a low blood flow to the tissue, especially when the concentration of the drug in plasma is not maintained (eg, after a single IV injection). On the other hand, if the plasma level is maintained (eg, by repeated doses or continuous infusion) the drug will slowly accumulate in tissues with a low blood flow and a high partition coefficient for the drug. Later, when administration of the drug is discontinued, blood flow will limit the rate of drug removal from the tissue which will then serve as a reservoir to maintain low, but persistent plasma levels of the drug.

Storage—The uptake of drugs by nonresponsive tissues reduces their pharmacological effect by lowering the concentration of drug in plasma, and in turn, at sites of action. However, drugs stored in nonresponsive tissues that do not metabolize or excrete them retain their pharmacological potential and can manifest it when they re-enter the circulation and are redistributed to sites of action.

Special Barriers—There are a number of special considerations in terms of the rate and extent of entry of certain drugs into certain tissues. The most notable of these is the concept of the *blood-brain barrier*. Rather than a single anatomical or functional feature of the cerebral capillaries, this concept embodies a number of mechanisms the net effect of which is to limit the amount of drug entering the central nervous system (CNS) from plasma. Generally speaking, the same physicochemical properties of drugs that limit their penetration of parenchymal cellular membranes also limit the entry of drugs into the CNS (ie, low lipoidal

TABLE 2
Factors Affecting Drug Concentration at Sites of Action in Fetus

Placental factors
Permeability coefficient for drug
Placental metabolism of drug
Integrity of placenta
Maternal-fetal concentration gradient
Plasma protein binding of drug
Maternal factors
Placental blood flow
Half-time of drug in arterial plasma
Fetal factors
Umbilical blood flow
Hepatic metabolism
Umbilical vein to liver
Dilution in blood volume
Uptake by nonresponsive tissues (storage)
Excretion (amniotic fluid)

solubility, ionization, large molecular size, or binding to large molecules).

Another so-called "barrier" is the *placenta,* which restricts the entry of certain drugs into the fetus. It is now recognized that there are a number of mechanisms operating to limit the concentrations of drugs achieved in the fetus (table 2). For example, the drug may be metabolized in the placenta or in the fetal liver through which most of the umbilical venous blood flows before entering the systemic arterial circulation of the fetus.

Two factors are especially important in determining the total amount of drug transferred from the mother to her fetus. One is the *rate* of drug penetration across placental membranes; it is determined primarily by the physicochemical characteristics of the drug and the integrity of the placenta The other is the *duration* of exposure of the fetal circulation of pharmacologically significant concentrations of the drug in maternal plasma.

If the maternal plasma levels fall rapidly to a low level (eg, following a single IV bolus dose of modest size), there will be only a brief exposure of the fetal circulation to pharmacologically effective concentrations and only a small amount of the drug will enter the fetal circulation (fig 4A). Moreover, the concentration of drug achieved in umbilical venous blood will be progressively decreased by dilution in the total circulating blood volume of the fetus and by distribution to sites of storage, and possibly by metabolism and excretion in the fetus. The amount of drug reaching its sites of action is thus reduced considerably, even for drugs able to penetrate placental membranes rapidly.

On the other hand, even those drugs with a very slow rate of penetration of placental membranes can achieve high levels in the fetus as long as their concentration in maternal plasma is maintained by continuous infusion (fig 4B) or repeated administration (fig 4C) of the drug to the mother.[4]

Elimination of Drug from the Body

The processes of drug elimination include biotransformation and excretion. They begin almost immediately after an IV injection when the circulation of plasma distributes some of the drug to organs able to metabolize the drug or excrete it from the body. Among the organs of elimination, the liver is the principal site of biotransformation and the kidney is primarily responsible for the excretion of most noninhaled drugs and their metabolites. However, other organs may also participate in the elimination of certain drugs (eg, gastrointestinal excretion of morphine).[5] The factors influencing the rate of hepatic biotransformation and renal excretion are summarized in table 3.

Biotransformation

Biotransformation of the drug to a metabolite essentially removes the drug from the body. However, the consequences of drug metabolism in terms of the effects observed following drug administration depend on the pharmacological activity of the individual metabolite(s). Metabolites may be active or completely inactive. Active metabolites may be more or less potent than the parent drug and may have qualitatively similar or dissimilar actions. The disposition of metabolites in the body is governed by the same principles described for the parent drug, but in almost all cases, the actual kinetics of distribution and elimination of the metabolite differ from those of the parent drug. This is to be expected since each metabolite differs from the parent drug in its physicochemical properties. It is absolutely essential that the analytical procedures employed in pharmacokinetic studies measure the parent drug and its metabolite(s) separately.

The rate of biotransformation of most

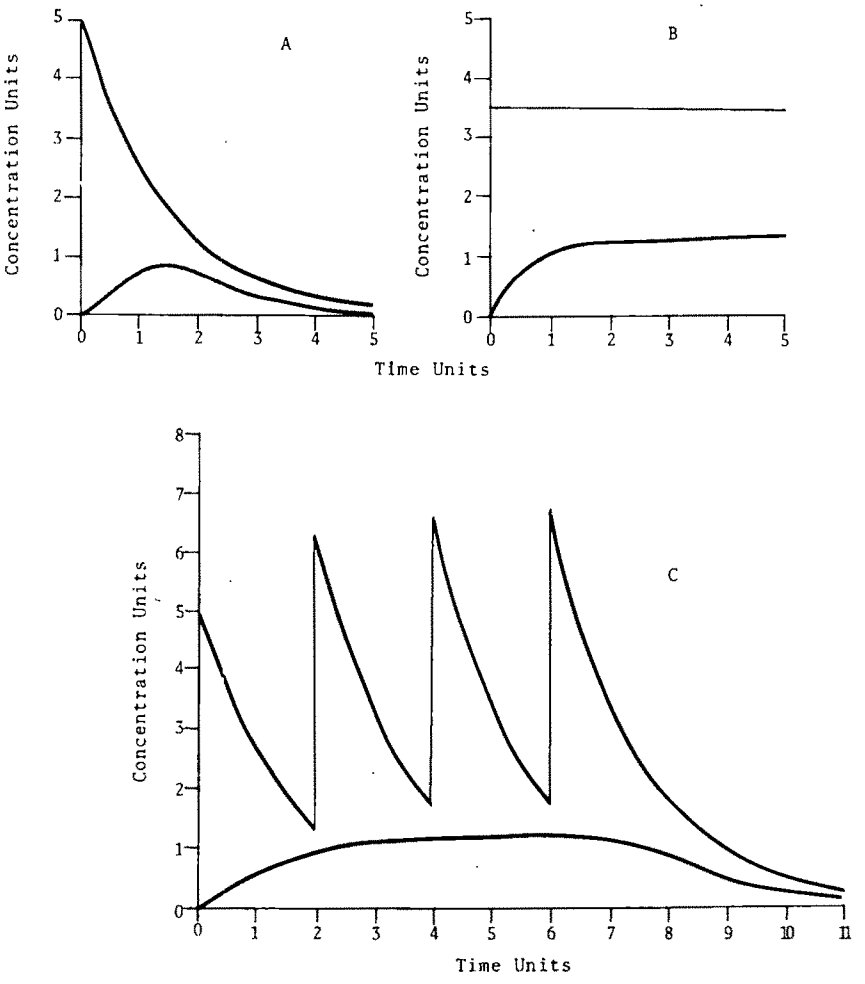


FIG 4. Effect of duration of elevated maternal plasma levels (top lines) of a drug on its plasma levels in the fetus (bottom lines). (A) If maternal plasma levels fall rapidly after a single IV bolus injection of the drug, relatively low concentrations are achieved in the fetus. (B) If maternal plasma levels are maintained (eg, by an IV infusion), fetal concentrations of the drug will progressively increase until they equilibrate with the plasma levels in the mother. (C) Repetitive administration of IV bolus doses leads to accumulation of the drug in both the mother and the fetus.

drugs is determined by the concentration of the drug at the site of drug metabolism and by the intrinsic rate of the biotransformation process. In other words, most drug metabolism follows first-order kinetics, and a *constant fraction* of the available drug is metabolized in a given time period. The concentration of drug at the site of the metabolism is determined by its concentration in plasma and the blood flow to the liver through both the hepatic and portal vessels. The intrinsic rates of biotransformation reactions are determined by a large number of factors affecting enzymic activity and cofactor availability (eg, genetics, presence of other drugs, nutrition, hypoxia). Some reactions are so efficient that plasma passing through the liver can be completely cleared of its drug content, both the free and protein-bound forms.

Under circumstances in which the concentration of drug to be metabolized exceeds the capacity of the biotransformation process (eg, saturation of the enzyme) the rate of drug elimination follows zero-order kinetics, that is, it is determined solely by the intrinsic rate of the process. Under such conditions, a *constant amount* of the drug rather than a constant fraction of the available drug is metabolized in a given period of time. The pharmacokinetics of ethanol elimination are zero order for this reason.[6]

Excretion

Excretion of drugs in urine by the kidney removes them from the body. The rate

TABLE 3
Influences of Drugs on Hepatic Biotransformation and Urinary Excretion

Hepatic biotransformation influenced by:
Hepatic blood flow
Portal blood flow
Absorption of drug administered enterally
Enterohepatic circulation
Microsomal drug metabolizing activity
Genetics
Cofactor supply
Inhibitors, including alternate substances
Inducers
Urinary excretion influenced by:
Renal blood flow
Glomerular filtration rate
Free drug
Tubular secretion
Free and bound drug
Inhibitors of transport
Metabolism of drug in renal cells
Tubular reabsorption
Urine flow
Urine pH

of excretion is determined by renal blood flow and by the rates of 3 renal processes: glomerular filtration, tubular secretion, and tubular reabsorption. Drug that is not bound to plasma protein passes through the glomerulus at a rate dependent on its concentration and on the volume of the glomerular filtrate. Tubular secretion involves active transport processes which are selective for certain drugs and drug metabolites; often they are so efficient that both the free and protein-bound forms of the drug can be removed from the renal tubular plasma. These active transport mechanisms can be affected by a number of factors (eg, transport inhibitors, hypoxia).

Tubular reabsorption removes drug that has entered tubular fluid by glomerular filtration and tubular secretion. Reabsorption is most efficient for drugs readily able to penetrate cellular membranes. The reabsorption of some drugs is so extensive that there is very little loss of the unchanged drug from the body in urine. One frequent consequence of biotransformation is the production of more polar metabolites, less able to penetrate cellular membranes, less susceptible to renal tubular reabsorption, and, therefore, more readily excreted in urine. A number of variables can affect the rate of reabsorption (eg, pH and rate of tubular urine flow)

Plasma Protein Binding Versus Elimination—Most drugs are reversibly bound to plasma proteins by weak forces (ionic, hydrogen, or van der Waals bonds) and the drug-protein complex can dissociate very rapidly (milliseconds) in response to a reduction of the concentration of free drug.

$$\text{Drug} + \text{Protein} \rightleftharpoons \text{Drug-protein}$$

Free drug is rapidly removed from plasma by certain organs having very efficient uptake processes (eg, renal tubular secretion, hepatic biotransformation). As a result, it is possible for the plasma perfusing those organs to be cleared completely of their drug content, both the free and protein-bound forms. Under such conditions protein binding of the drug does not impede its elimination from plasma but may even facilitate its elimination from the body by retaining more of the drug in plasma and delivering it to the organs of elimination.

KINETICS

In the above discussion of factors influencing the concentration of drug in plasma, the emphasis has been on the *rates* at which a drug is taken up by tissues and eliminated from the body. *Kinetics* can be defined as the rate of change and can be expressed as units of amount per unit of time (eg, percent per hour, micrograms per minute).

Linear Kinetics

In most cases, the processes by which a drug enters tissues (eg, diffusion) and is eliminated from the body (eg, urinary excretion) can be described by first-order kinetics. That is, the rate of change in the concentration of drug is dependent on the drug concentration. The relationship can be expressed by the equation

$$\frac{dC}{dt} = -kC \qquad [1]$$

where C = concentration of drug

k = first-order rate constant

t = time.

That is, the rate of change in drug concentration per unit of time is equal to the drug concentration multiplied by the rate constant for that particular first-order process. A negative sign indicates that the drug concentration is decreasing with time. In the case of IV administered drugs, the concentration in plasma begins to decrease as soon as drug administration is complete and con-

tinues until all of the drug has been eliminated from the body.

There are several important and practical points to be remembered about this equation.

1. The rate of drug elimination is proportional to the drug's concentration; the higher the concentration, the greater the absolute amount of drug eliminated per unit time. In other words, a *constant proportion* of the drug (rather than a constant amount) is eliminated per unit time (eg, 50% per hour).

2. It is possible by mathematical manipulations to convert equation [1] to

$$\log C_t = \log C_o - \frac{kt}{2.303} \qquad [2]$$

where C_t = concentration of the drug at any time (t) after the start of the process at time zero

C_o = concentration of the drug at time zero

2.303 = a constant required for the conversion to common logarithms

k = rate constant for the first-order process, preceded by a negative sign because the process is reducing the drug concentration.

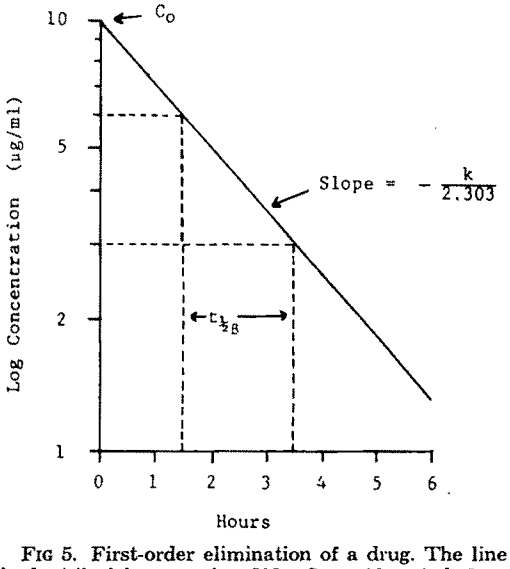


FIG 5. First-order elimination of a drug. The line is described by equation [2]. C_o = 10 µg/ml, k = 0.35 hr^{-1} $t½\beta$ = 2 hours.

This equation can be represented graphically as a straight line when log concentration (log C_t) is plotted against time (t) (fig 5). The intercept of the line with the ordinate at time zero is designated as C_o. The slope of the line is given by $(-\frac{kt}{2.303})$ and is constant over time; for this reason, the process is said to follow "linear kinetics."

3. The effect of multiple first-order processes acting simultaneously on the same quantity of drug can be represented mathematically by the algebraic sum of their individual rate constants:

$$k_n = k_1 + k_2 + k_3 \ldots\ldots$$

Thus, for example, one elimination rate constant (k_{el}) may represent the combined effects of biotransformation of the drug in the liver by a first-order process and renal excretion of the drug by diffusion through the glomerulus, another first-order process.

4. A first-order process is often described in terms of its *half-time* ($t½$) rather than by its rate constant (k). Since a constant proportion or fraction of the drug is eliminated per unit time, it has become a common practice to specify the rate in terms of the time required for one-half of the available drug to be eliminated. The half-time of a first-order process can be estimated graphically by choosing any point on the *straight line* and measuring the time interval to a point representing one-half that value on the same straight line (fig 5). The half-time can also be calculated from the equation:

$$t½ = \frac{0.693}{k} \qquad [3]$$

where k is the first-order rate constant and 0.693 is the natural logarithm of 2 (ln 2).* It should be noted that multiple numbers of half-times are required for completion of a process. For example, if 50% of the drug is eliminated in 30 minutes (50% remains), then an additional 25% (ie, 50% of 50%) will be eliminated in the next 30 minutes (25% remains), and another 12.5% (ie, 50% of 25%) will be eliminated in the next 30 minutes, etc. The time in which 50% of the available or remaining drug is eliminated is referred to as the half-time of elimination. About 5 half-times are required to eliminate 96.9% of the drug (table 4).

*Natural logarithms allow the semilogarithmic rate constant (k) to be converted to arithmetic terms.

TABLE 4
Relationship of Half-Times to Amount of Drug Eliminated by a First-Order Reaction

Cumulative No. of half-time.	Fraction of initial amount remaining	% of initial amount eliminated
0	1	0
1	1/2	50
2	1/4	75
3	1/8	87.5
4	1/16	93.8
5	1/32	96.9
6	1/64	98.4

Nonlinear Kinetics

The rate of elimination of a few drugs (eg, ethyl alcohol) from plasma is not first-order nor is it proportional to the concentration of the drug. In most of these cases, elimination follows zero-order kinetics, that is, the rate of change in drug concentration is independent of the concentration of the drug. A *constant amount* of the drug (rather than a constant proportion) is eliminated per unit time (eg, μg/min).

The most common reason for drug elimination by zero-order kinetics is that the major mechanism for elimination becomes saturated with the drug and proceeds at its maximum possible rate.

Michaelis-Menten Kinetics

Virtually all biotransformation processes are catalyzed by specific enzymes with a limited capacity for the drug. Some drugs are transported across biological membranes by a carrier with a limited capacity. The rate of change in drug concentration in these circumstances is most accurately described by the Michaelis-Menten equation:

$$-\frac{dC}{dt} = \frac{Vm\,C}{Km + C} \qquad [4]$$

where C = concentration of drug
t = time
Vm = a constant representing the maximum rate of the process
Km = Michaelis constant, the drug concentration at which the process proceeds at exactly one-half of its maximal possible rate.

Michaelis-Menten kinetics are usually applied to studies of isolated tissues in which the concentration of drug can be varied over a much larger range than is safe for the intact animal or human. Michaelis-Menten kinetics are especially useful in the characterization of a single, specific enzyme or transport carrier in vitro. The complexities of the intact body preclude such characterizations in vivo.

In the intact subject, the more narrow range of useful and tolerable drug concentrations usually fits one of two special cases of Michaelis-Menten kinetics.

1. The concentration of drug is so much *smaller* than the Km that the term C can be eliminated from the denominator of equation [4]. Since Vm and Km are both constants, they can be represented by another constant (ie, $\frac{Vm}{Km} = k$), and the equation becomes identical to that of a first-order process (equation [1]).

2. The concentration of drug is so much *larger* than the Km that the term Km can be eliminated from the denominator of equation [4]. When this is done, the term C can be canceled from both the numerator and denominator and this leaves the expression:

$$-\frac{dC}{dt} = Vm \qquad [5]$$

which means the rate of drug elimination is equal to a constant and follows zero-order kinetics.

It is conceivable that the pharmacokinetics of any one drug could change from zero- to first-order or vice versa when the dose is varied over a very large range, and for this reason, it is highly desirable to perform pharmacokinetic studies with doses at the extremes of the range employed clinically.

PHARMACOKINETIC MODELS

It is obvious that a large number of factors influences the concentration of drug in plasma. In the practical world of clinical medicine it is not possible or necessary to keep track of all these individual variables. Moreover, not all of the factors are equally important for each and every drug. Therefore, it is useful to summarize the pharmacokinetics of individual drugs in the simplest manner that will provide the information necessary for the identification of the most important factors and will allow the consequences of clinically encountered variables to be predicted.

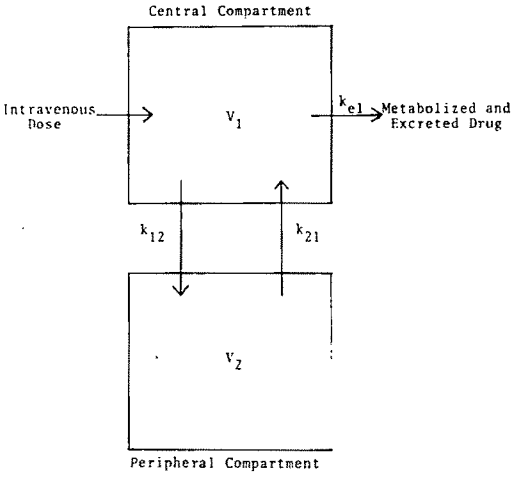


FIG 6. Two-compartment open model of drug disposition. The IV administered drug equilibrates between the central and peripheral compartments but is eliminated only from the central compartment. See text for definitions of abbreviations.

Pharmacokinetics has been simplified for many drugs by considering the body to comprise a limited number of compartments. The two-compartment model (fig 6) has proven useful for some drugs and it can be used to demonstrate the basic concepts that also apply to more complex models. In this model, the drug is introduced directly into the central compartment by an IV injection. The drug distributes to a peripheral compartment and is eliminated from the body only by way of the central compartment. We can interpret these pharmacokinetic processes by considering their effects on concentrations of the drug in plasma.

Plasma in the circulating blood is in the central compartment and is considered to be representative of all components of the central compartment. The highest concentration of drug in plasma (C_{P_0}) will occur at time zero, immediately after IV injection, and will be determined by the size of the IV dose and the volume of the central compartment (V_1) in which it is diluted:

$$C_{P_0} = \frac{\text{Dose}}{V_1} \qquad [6]$$

The *central compartment* is defined only in terms of its volume (V_1), which is an apparent volume based on the above relationship and only rarely corresponds to actual anatomical volumes. Generally speaking, the central compartment consists of plasma and those tissues in which the uptake of drug is so rapid that they cannot be distinguished from plasma pharmacokinetically. For drugs able to penetrate membranes rapidly, the central compartment usually includes the vessel-rich group of tissues such as brain, heart, lung, liver, and kidney. However, studies of the actual uptake of a particular drug by individual tissues are necessary before any of them can be assigned to a specific compartment in the pharmacokinetic model for that particular drug. For practical purposes, this is usually not necessary.

In addition to dilution within the central compartment, the plasma concentration of a drug is affected by its rate of entry into the peripheral compartment (*distribution*) and by its rate of *elimination* from the body. Both of these processes, that is, distribution and elimination, begin immediately as the drug enters the circulation, and initially, both contribute to a progressive lowering of the plasma concentration of the drug. It happens for most drugs that the contribution of the distributive processes to the decline of plasma levels of the drug is relatively short lived. This is because the exchange of drug between the central and peripheral compartments is an equilibrium process dependent on the concentration gradient of the drug. Initially, the gradient is from the central to the peripheral compartment at the maximum possible rate (k_{12}) as determined by the drug's permeability coefficient and blood flow to the tissue. With time, the gradient decreases as the concentration of drug builds up in the peripheral compartment and continues to decline in the central compartment. Eventually the net exchange of drug will be zero (equilibrium) and then the exchange will be reversed (ie, from peripheral to central) as the drug continues to be eliminated from the central compartment by biotransformation and excretion. Past the equilibrium point, the return of drug from a peripheral compartment tends to maintain rather than reduce plasma levels.

Even though the distributive processes to the *peripheral compartment* may be relatively short lived, they exert a major influence on plasma levels of many drugs. The peripheral compartment is defined only in terms of its apparent volume (V_2). A very large V_2 suggests extensive uptake of the drug by those tissues and organs composing the peripheral compartment. Again it should be noted that specific tissues can be assigned to a peripheral compartment only by studies of the kinetics of their individual uptake of drug, and this is seldom necessary for practical purposes. The practical significance of

the peripheral compartment relates to the following: (1) Rapid (large k_{12}) and extensive (large V_2) uptake of drug by a peripheral compartment contributes to a rapid reduction of plasma levels of the drug (2) Beyond the equilibrium point ($Cv_1 = Cv_2$), re-entry of drug into the central compartment from the peripheral compartment can maintain drug levels in plasma. (3) If the rate of drug return from the peripheral compartment is slow (small k_{21}), it can limit the ultimate rate of elimination of the drug from the body. (4) Residual drug present in the peripheral compartment at the time of a repeat injection will diminish the effect of distributive processes on the reduction of drug levels in plasma and lead to more intense effects of the drug (ie, drug accumulation).

Drug Elimination—Drug elimination from the body by biotransformation and excretion begins as soon as the drug appears in the circulating plasma and continues until the entire dose is eliminated from the body. Although several different processes may be involved, their combined effect can be described by a single constant (k_{el}), since for most drugs, the individual processes each follow first-order kinetics and they are additive in their effect on plasma levels of the drug (ie, $k_{el} = k_1 + k_2 + k_3 \ldots$, where each k_n value is for a specific process). Again it should be noted that the ultimate elimination of a drug from the body occurs only by way of the central compartment in this model. Thus, drug in the peripheral compartment must re-enter the central compartment to be eliminated. If k_{21} is smaller than k_{el}, the rate-limiting step of the final elimination of drug from the body will be determined by reuptake from tissue rather than the processes of biotransformation and excretion.

Elimination of the drug from the body is assumed to be irreversible. Biotransformation reactions are essentially nonreversible.* Very little drug can be reabsorbed from urine flowing along the ureteral-bladder-urethral pathway.

*Metabolites of drugs may be excreted into bile, in which they enter the duodenum and flow along the intestine. The metabolites may be absorbed from the intestinal tract or some conjugated drugs may be hydrolyzed (eg, by E. coli glucuronidase in the colon) and the released ("unchanged") drug may be absorbed. The contribution of enterohepatic circulation to plasma levels of drug has been recognized by a temporary rise interrupting the otherwise progressive decline of drug concentrations in plasma (eg, diazepam).[5]

PLASMA CONCENTRATION VERSUS TIME

For the vast majority of drugs administered IV, a graphic representation of the change in plasma levels of the drug over time can be constructed by plotting the logarithm of the concentration on the ordinate against time on the abscissa (fig 7). Logarithms provide a convenient means of managing the two- or three-fold range of plasma concentrations encountered in plasma after an IV dose, and they also are appropriate for the processes of distribution and elimination, most of which can be described by first-order kinetics.

The typical graph is a biexponential curve representing two distinct phases in the decline of the plasma concentration of a drug following a single IV dose. The terminal ("elimination") portion of the curve is linear and can be described by its slope (β)

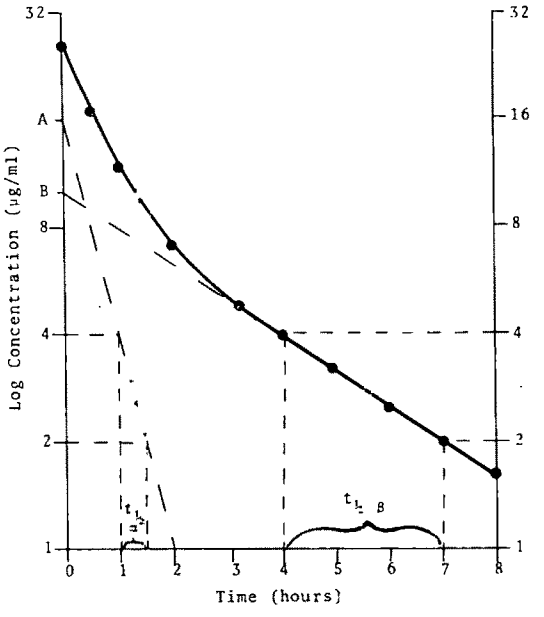


FIG 7. Plasma log concentration vs time relationships for a drug administered IV at time zero. The solid curved line connecting the dots represents the experimentally measured concentrations. Note that the terminal portion of the curve is linear and can be described by its slope (β) and its intercept (B) when the line is extrapolated back to the ordinate. The $t_{1/2}\beta$ is 3 hours. If the values represented by the extrapolated portion of the β line are subtracted from the actually measured values on the initial curved portion of the solid line, another straight line can be plotted with a slope (α) and an ordinal intercept (A). The $t_{1/2}\alpha$ is 0.5 hours.

Note that the concentration is reduced by more than 70% of its initial value in the first 2 hours, but 8 hours are required to eliminate 94% of the drug from plasma.

and its intercept (B) when the line is extrapolated back to the ordinate. Since the elimination processes begin almost as soon as the drug is injected, it is justifiable to extrapolate the line to zero time. Extension of the line beyond the last data point is not justified, however, since the kinetics may change at later times.*

The initial ("distribution") portion of the biexponential curve represents the combined effects of distribution and elimination processes on plasma levels of the drug. The actual kinetics of distribution can be estimated merely by subtracting the contribution of elimination processes represented by the extrapolated line of the "β" or elimination phase. Subtraction analysis yields another straight line (as shown in fig 7) characterized by a slope (α) and an intercept with the ordinal axis (A); this line represents the first-order kinetics of distribution. In other words, the complex curvilinear relationship between log concentration and time can be described by two individual lines, α and β, which represent, respectively, the distributive and elimination phases of drug disposition in a two-compartment model.

The complete biexponential curve can be described by the equation: †

$$C_{Pt} = A\ exp^{-at} + B\ exp^{-\beta t} \qquad [7]$$

where C_{Pt} = concentration in plasma at any time (t) after an IV injection

A = ordinal intercept and α = slope of the line representing the distribution phase

B = ordinal intercept and β = slope of the line representing the terminal elimination phase

exp = exponential functions of the rate constants represented by α and β and time (t)

The coefficients A, B, α, and β are hybrids; that is, their actual values are determined by both distribution and elimination processes. They can be manipulated mathematically to provide estimates of distribution volumes and the first-order rate constants for distribution and elimination processes for a two-compartment open model like that shown in fig 6. In a more practical vein, they can be used to predict drug accumulation with repeated administration and to calculate the rate of IV infusion required to maintain a constant plasma level of a drug and presumably a constant intensity of its action (see Appendix). *Half-time* is more commonly used than are the coefficients α and β to express the rate of decline of drug concentrations in plasma. Each half-time value must be specifically identified with the particular process or phase to which it applies (eg, $t_{1/2\alpha}$ refers to the half-time of the initial distributive phase of drug disposition).

CLINICAL APPLICATIONS OF PHARMACOKINETIC DATA

Duration of Drug Action Versus Dose—Fentanyl is a narcotic analgesic administered IV as an anesthetic supplement. In both man and dog a single IV injection of a moderate dose produces a short-lasting depression of respiration (approximately 60 minutes), whereas repeated administration of the same size dose leads to more prolonged depression. Examination of the pharmacokinetics of fentanyl in the dog provides an explanation (fig 8).

The recovery from ventilatory depression paralleled the decline in plasma concentrations of fentanyl. The threshold concentration of fentanyl in plasma for ventilatory depression in the anesthetized dog was approximately 1 ng/ml. Plasma levels fell below threshold 60 minutes after a single IV injection of 10 μg/kg, but residual fentanyl was present in plasma for a considerably longer time due to the prolonged terminal elimination phase. When the same dose was repeated at 90-minute intervals,* each successive dose led to progressively

*For example, an elimination process may be saturated and follow zero-order kinetics when the drug concentrations in plasma are high. As the concentrations decline and the process is no longer saturated, its rate of eliminating the drug will correspond to first-order kinetics. Another possible cause for later changes in kinetics is that one or more of the elimination mechanisms drops out and the remaining ones assume dominance in the ultimate elimination of all drug molecules from the body.

†Note that equation [7] can be converted to common logarithms (base 10) for convenience of calculations:

$$\log C_{Pt} = (\log A - \frac{at}{2.303}) + (\log B - \frac{\beta t}{2.303})$$

The latter form is the same as that shown in equation [2], and represents the additive effects of separate first-order processes (ie, distribution and elimination) on the drug concentration in plasma.

*In clinical practice accumulation would be even greater because the dosage interval would have to be shorter in order to maintain the effect beyond 60 minutes. Ninety minutes was chosen for experimental reasons.

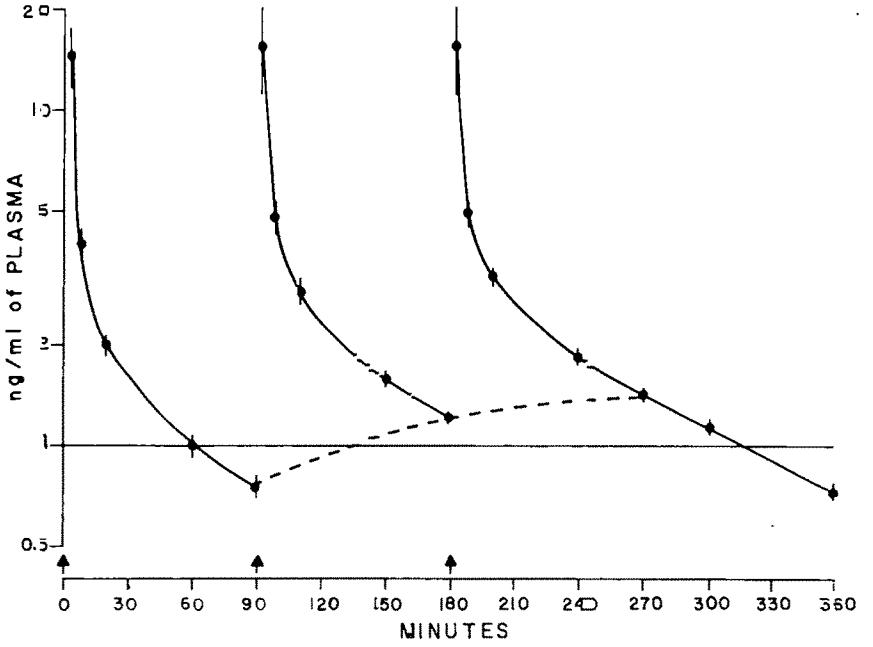


FIG 8. Plasma concentrations of unchanged fentanyl following each of 3 successive doses (10 μg/kg) administered IV at 90-minute intervals. Data points represent the mean ± SEM for 4 dogs. The dotted line connects values for successive 90-minute intervals and indicates cumulation of fentanyl with repeated doses. The horizontal line represents the threshold concentration for fentanyl-induced ventilatory depression (Hug et al[8]).

more intense and longer lasting ventilatory depression which was associated with higher plasma levels that remained above the threshold concentration for longer periods of time. In other words, successive doses of fentanyl added to the residual fentanyl in the body.[8] The same phenomenon of accumulation occurs with repeated doses of thiopental. Each successive dose produces more prolonged periods of unconsciousness, until an apparently short-acting drug (ie, after a single dose) becomes a long-acting one.[9] (The potential lessening of effect due to the development of acute tolerance to thiopental is minor compared to the degree of accumulation that occurs and is evident in fact by the prolonged recovery time.) The degree of accumulation of any drug can be calculated if the volume of distribution (V_d), slope of the terminal elimination phase (β) dose, and dosage interval are known (see Appendix).

Another pharmacokinetic aspect of drug dose vs duration has to do with attempts to lengthen the duration of effect by giving a larger initial dose. The consequences in the case of fentanyl in the dog are illustrated in fig 9. A 10-fold increment in dose produced an 8-fold increase in the *time* plasma levels remained above the threshold concentration. The concentration of fentanyl in plasma was also increased by a factor of 10 and presumably the intensity of its action was similarly increased.[10] Similar relationships for thiopental are the likely explanation for the many deaths due to this drug when attempts were made to lengthen the duration of its anesthetic action by increas-

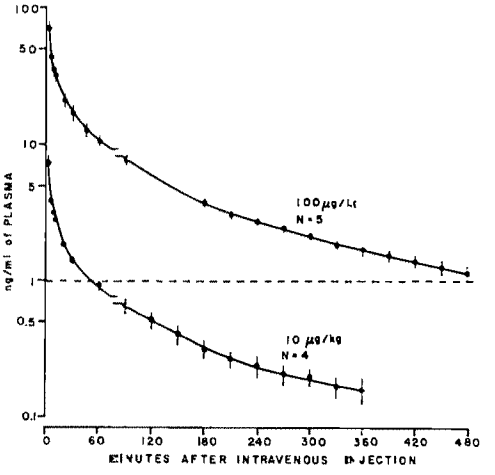


FIG 9. Concentrations of unchanged fentanyl in plasma after different doses. Each data point represents the mean ± SEM for the number of animals indicated by *N*. The lines were drawn by nonlinear least squares analysis of the mean data points for each dose (Murphy et al[10]).

ing the size of the dose injected for induction of anesthesia.[11,12] The larger the initial dose, the greater the plasma concentrations, and the more intense the drug effects on *all* organs. In the case of thiopental, marked depression of myocardial function led to severe hypotension and death while the objective was to produce a longer duration of anesthesia.[13] Pharmacokinetically, it would be wiser to administer smaller incremental doses or even to infuse the drug continuously in order to maintain anesthesia while avoiding toxicity.[14]

The full advantages of pharmacokinetic data have yet to be realized in most anesthetic practices. An example of the potential usefulness of pharmacokinetic information is found in the current use of IV lidocaine to control cardiac dysrhythmias. By combining an initial IV bolus dose with a continuous IV infusion, it is possible to establish an effective and safe level of lidocaine rapidly and to maintain it as long as necessary without the development of toxicity.[15] There is every reason to believe that the same pharmacokinetic principles can be applied to IV anesthetic drugs for the rapid introduction and maintenance of a *controlled* intensity of drug action. Of course, allowance has to be made for changing anesthetic requirements (eg, with differing degrees of surgical stimulation). Increased drug action can be produced rapidly with IV drugs by administering additional bolus doses or by speeding the infusion rate. The rate of response to slowing or stopping the infusion depends primarily on the rate of drug elimination (β). The most rapid decreases in effect are obtained with drugs having the shortest half-times for the terminal elimination phase ($t_{1/2\beta}$). In contrast to inhalational anesthetics, the elimination of IV drugs cannot be augmented by the anesthetist under the usual clinical conditions. Consequently, the use of IV drugs requires greater precision in estimating anesthetic depth and in anticipating changing anesthetic requirements. Titration of dosage to produce minimally sufficient drug concentrations and effect is necessary in order to minimize the time for recovery.

Variability in Responses to Drugs—Many unusual responses to drugs, especially those manifest as a change in the intensity and duration of drug action, can be explained by alterations in the disposition of the drugs in the body. Pharmacokinetic principles and methods can be applied to the identification of the responsible factors. Such factors as drug interactions,[16] disease states,[17] age,[18] and differences in body composition (eg, lean vs obese[19]) are known to alter drug disposition in the body and to affect the actions of drugs. However, very few studies to date have involved parenterally administered anesthetic drugs and their adjuvants. Considering the well-documented alterations of circulatory, hepatic, and renal functions by potent inhalational anesthetics, it is not hard to imagine that general anesthesia itself may affect the distribution and elimination of noninhaled drugs administered in the perioperative period.

Animals Versus Man—Often the differences between species in their response to drugs is a quantitative one that can be explained or predicted on a pharmacokinetic basis. In such cases, the availability of comparative pharmacokinetic data may expand the application of data from experimental animals to man.

LIMITATIONS OF PHARMACOKINETICS

There are a number of limitations to the applications of pharmacokinetics, and in addition, there are some rather widespread misconceptions about the interpretation of pharmacokinetic data.

Half-Time Versus Half-Life — Strictly speaking, half-life refers to the total dose or amount of drug in the body and is equal to the time required for elimination of one-half of the total dose of the drug from the body. In some cases, the half-time of the terminal elimination phase for the drug in plasma ($t_{1/2\beta}$) corresponds to the half-life of the drug in the whole body. However, in situations where the decline of drug concentrations in all tissues does not parallel its decline in plasma, $t_{1/2\beta}$ will not be an accurate estimate of half-life. In order to avoid confusion, it is necessary to identify specifically both the substance and the process when stating its half-time (eg, thiopental $t_{1/2\beta}$ or the half-time for the terminal elimination of thiopental from plasma).

Nonlinear Kinetics—Not all distribution and elimination processes follow first-order kinetics with fixed-rate constants. Although nonlinear processes are exceptions to the rules and principles summarized in this article, some important examples are known. The kinetics of ethanol metabolism are zero-order, ie, a constant amount rather

than a constant fraction of ethanol is eliminated in any given unit of time.[6] Kinetics can be dose dependent if the process becomes saturated at higher concentrations of the drug. Under such circumstances, first-order kinetics will apply at lower concentrations and zero-order kinetics will be exhibited at high concentrations.

Pharmacokinetics Versus Pharmacologic Effects—It is important to note that meaningful pharmacokinetic-drug effect relationships depend on two conditions: (1) the effect of the drug is proportional to its concentration at its site of action, and (2) the rise and fall of drug concentrations at the site of action parallel the rise and fall of plasma concentrations. The concentrations of drug at the site of action have to be *proportional* but not necessarily equal to those in plasma. One frequently occurring deficiency of pharmacokinetic investigations is the lack of a demonstration of the relationship between plasma concentrations of the drug and the intensity of its actions. If in fact there is no relationship, then the pharmacokinetic data are of little practical use to the clinician. (On the other hand, the lack of relationship should stimulate the investigator to find out the reasons drug effects do not correspond to drug concentrations.) There are several possible explanations for a lack of correspondence between pharmacokinetics and drug actions.

(1) The drug may be biotransformed to a pharmacologically active metabolite. The intensity of effect will then be proportional to the concentrations of the metabolite and the drug, if both are active. A specific analytical method for the drug should not measure the metabolite simultaneously with the drug. The kinetics of elimination of the drug and its metabolite will differ. For one thing, the physicochemical properties of the metabolite differ from those of the parent drug; therefore, it is expected that their patterns of distribution and elimination will also differ. Another important consideration is that metabolite will continue to be added to plasma as long as some drug remains to be transformed. For example, diazepam is metabolized by N-demethylation to desmethyldiazepam, which is a potent depressant. Desmethyldiazepam accumulates in plasma as the levels of diazepam continue to decline.[7,20a,20b]

Another possibility is that the active metabolite is formed at the site of action and although the rate of its formation may be proportional to the concentration of drug at the site of action, the kinetics of elimination of the metabolite from the site of action may differ from those of the parent drug.

(2) Alterations in the plasma levels of a drug may not be immediately reflected by changes in the concentration of drug at its site of action. This can occur with drugs that only slowly penetrate the membranes separating their site of action from plasma. For example, the decline of morphine levels in the central nervous system is slower than their elimination from plasma.[21,22] As a result, the effects of a single dose of morphine last longer than those of an equivalent dose of fentanyl even though the plasma $t_{1/2\beta}$ is shorter for morphine than for fentanyl.[8,21] Discrepancies between the rates of change of drug levels in plasma and at sites of action can also occur if the drug binds irreversibly with its receptor, usually resulting in the persistence of its effect beyond the time in which it is eliminated from plasma.

(3) If the dose of drug is very large, it may produce drug concentrations in excess of those needed to saturate drug receptors and to produce a maximum effect. In such circumstances, the relationship between drug concentration and effect will be obscured until drug concentrations are reduced below the receptor-saturation level.

(4) Almost all methods of drug analysis measure the total drug in plasma and not just the diffusable form which is able to penetrate capillary and cellular membranes. The methods do not distinguish between protein-bound and free drug nor between ionized and unionized forms of the drug. If the amount of diffusable drug is very small relative to the total amount of drug, small changes in the degree of protein binding (eg, alterations of protein concentration by blood loss or hemodilution) or the degree of ionization (eg, hypo- or hyperventilation) may produce only a slight alteration of the total drug concentration in plasma (well within the limits of variability inherent in the analytical technic), but may lead to marked changes in the tissue levels of the drug and its intensity of action.

Technical Considerations — Analytical methods are crucial to the ultimate value of pharmacokinetic investigations. They must be sufficiently *sensitive* to detect the drug in plasma or other specimens taken long after administration of the drug, and they must be *specific* for the drug and ex-

clude drug metabolites and other extraneous substances found in the specimen.

Metabolites usually differ from the parent drug in both their pharmacologic activity and in their distribution and elimination from the body. If the analytical method measures the metabolites as well as the parent drug, the interpretation of the results is impossible. For example, morphine is efficiently metabolized by conjugation to morphine-glucuronide, a pharmacologically inactive metabolite that appears rapidly and in large concentrations in plasma.[23,24] Within 30 minutes after a single IV injection of a 0.15 to 2 mg/kg dose, the level of morphine-conjugate in plasma exceeds that of the unchanged and pharmacologically active morphine by 7-fold. This ratio between conjugated and unchanged morphine continues to increase beyond 30 minutes and has been reported to be as high as 24:1 at 8 hours after injection.[23-25] Radioimmunoassay technics for morphine have only a limited specificity for the unchanged drug;[26] therefore, a significant amount of conjugated morphine is included in the values reported for morphine analyzed by radioimmunoassay of plasma obtained at later times following morphine administration. The interpretation of pharmacokinetic studies based on radioimmunoassay technics is open to question,[27-29] unless the technic is modified to make it specific for the unchanged drug.[24]

Experimental Design—It is necessary to collect a sufficient number of plasma samples over a sufficiently long period (usually hours) to be reasonably certain that the terminal portion of the plasma log concentration vs time curve is linear and representative of the terminal elimination phase. Otherwise the entire mathematical expression of the pharmacokinetics of the drug in plasma will be wrong. (Remember that the determination of A and α for the distribution phase is based on the subtraction of the contribution of the terminal elimination phase.) As a consequence, all parameters of drug disposition will also be wrong and misleading to clinicians who use them to make predictions about dosage requirements, degree of accumulation, etc.

Of course, limitations in the sensitivity of the method of drug analysis may preclude measurement of the drug concentrations present in plasma several hours after a single IV dose. It may be possible to overcome these limitations by increasing the size of the single dose (providing the kinetics are not dose dependent and the dose is tolerated by the subject) or by infusing the drug continuously. In the latter circumstance, once the distribution phase is complete, a constant drug concentration will exist in plasma and the rate of drug elimination will equal the rate of its infusion.

SUMMARY

Drug disposition is determined by multiple complex processes acting simultaneously and interdependently. Pharmacokinetics offers a means of summarizing the combined effects of these many processes under specified conditions. Beyond that, pharmacokinetic concepts applied with an understanding of the basic processes of drug disposition make it feasible to predict and then to test experimentally the consequences of alterations in conditions of drug administration to patients. Clinical investigations of the disposition of drugs used by anesthesiologists should provide a basis for safer, more effective, and more efficient utilization of expensive and potent compounds used for anesthesia and disease therapy in the perioperative period.

On the other hand, it is important for the clinician to recognize the limitations of pharmacokinetics and to avoid pitfalls associated with misinterpretations of drug disposition data. To be of practical use, the relationships between drug effects and disposition must be understood. And it must be constantly borne in mind that pharmacokinetics is a descriptive science with a predictive value no more accurate or precise than the data on which the pharmacokinetic model is based, and often restricted in application to the specific conditions encountered in accumulating that data. There is a need for pharmacokinetic studies of IV anesthetic and adjuvant drugs under all types of clinical conditions.

APPENDIX

Two-compartment open model. Mathematical characterization of the log concentration vs time line (fig 7) provides the coefficients A, B, α, β. The value of these coefficients is determined by both distribution and elimination processes. The actual pharmacokinetic parameters for a two-compartment open model (ie, V_1, V_2, k_{12}, k_{21}, k_{el} as shown in fig 6) can be calculated according to the formulas below. The reader interested in the rationale and mathematical derivation of the formulas should consult

the texts by Gibaldi and Perrier[1] and by Wagner.[2]

$$V_1 = \frac{\text{Dose}}{A + B} \quad [8]$$

$$k_{el} = \frac{\text{Dose}}{\frac{A}{\alpha} + \frac{B}{\beta}} \quad [9]$$

$$k_{21} = \frac{\alpha\beta}{k_{el}} = \frac{A\beta + B\alpha}{A+B} \quad [10]$$

$$k_{12} = \frac{A \cdot B}{(A + B)^2} \cdot \frac{(\beta - \alpha)^2}{k_{21}} \quad [11]$$

The estimation of V_2 depends on an accurate estimation of the total apparent volume of distribution (V_d), since

$$V_2 = V_d - V_1 \quad [12]$$

V_d can be estimated most accurately during the steady-state condition of no net transfer of drug between the central and peripheral compartments. Maintenance of a steady state condition requires a constant IV infusion since the state of equilibrium between V_1 and V_2 is only momentary after a single bolus IV injection. Under steady state conditions,

$$V_{d(ss)} = V_1\left(1 + \frac{k_{12}}{k_{21}}\right) \quad [13]$$

and since $V_2 = V_d - V_1$, [14]

$$V_2 = V_1\left(\frac{k_{12}}{k_{21}}\right) \quad [15]$$

After a single IV dose, an estimate of V_d can be obtained from the equation:

$$V_{d(area)} = \frac{\text{Dose}}{\beta\left(\frac{A}{\alpha} + \frac{B}{\beta}\right)} \quad [16]$$

The denominator term $\left(\frac{A}{\alpha} + \frac{B}{\beta}\right)$ is taken as an estimate of the area under the total plasma concentration curve from zero (t_0) to infinity (t_∞). This term represents an attempt to account for the total amount of drug in the body at all times after distribution equilibrium has been obtained.[8]

Other Models — The two-compartment model has been applied effectively to many drugs administered IV by anesthesiologists. However, models of greater complexity are occasionally useful and may become more prevalent as sampling, analytical, and computing methods improve. Multicompartment models have already been proposed for fentanyl,[10,30] thiopental,[31,32] and the inhalational anesthetics.[33]

Clearance (Cl) — In pharmacokinetic terms, clearance refers to the volume of the central compartment from which a drug is entirely eliminated (or cleared) in a specified unit of time (generally, ml/min). In other words, it is an index of drug elimination from the central compartment based on k_{el}, whereas β or $t_{½\beta}$ depends on k_{12} and k_{21} in addition to k_{el}. Clearance is calculated as:

$$Cl = V_1 \cdot k_{el} \quad [17]$$

It should be noted that changes in clearance may occur as a result of an alteration of either V_1 or k_{el}, or both. Thus, a change in clearance associated with a disease process may result from impaired function of drug metabolizing or excreting mechanisms and/or from altered distribution of the drug. For example, drug may shift from the central to the peripheral compartment when its binding to protein in plasma is decreased as in hypoproteinemia. As a result, its clearance will tend to decrease.

Accumulation After Repeated Doses — The degree of accumulation of any drug in plasma can be calculated if its volume of distribution (V_d), the slope of its terminal elimination phase (β), and the dose and dosage interval are known:

$$\text{Average concentration in plasma during dosage interval} = \frac{\text{Dose}}{V_1 \cdot \beta \cdot \text{Interval}} \quad [18]$$

It is apparent that proportionally higher drug concentrations will be found in plasma if the dose size is increased or the dosage interval is reduced. Reducing the interval by one-half will double the average concentration. The average concentration will also be affected by changes in the apparent volume of distribution (V_d). Disease states such as shock, hypovolemia, edema, etc, can be expected to alter V_d as well as interfere with the processes contributing to the ultimate elimination of drug from the body (β).

Constant Intravenous Infusion — The steady state plasma level of a drug administered by constant IV infusion can be estimated from the pharmacokinetic parameters of a two-compartment model and the rate of infusion (Q). For long-term infusions (ie, 4 to 5 times $t_{½\beta}$), the steady state concentration of drug in plasma or central compartment (C_1^{ss}) is determined by the ratio

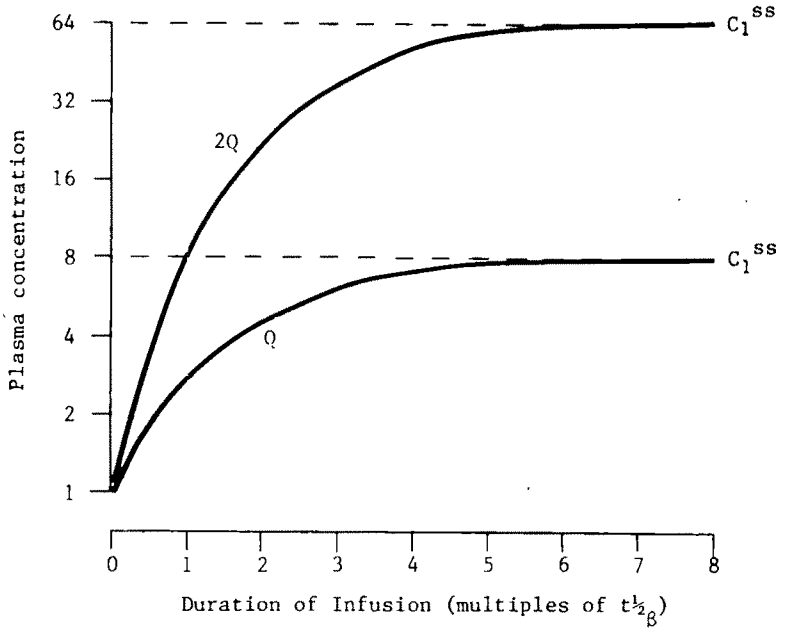


FIG 10. Plasma concentrations versus time during a constant IV infusion at two different rates (Q and 2Q). Note that at a rate of 2Q, any given concentration will be achieved faster, the steady state concentration will be double, but the rate of equilibration will be the same as for an infusion rate of 1Q.

of the infusion rate to the clearance rate as follows:

$$C_1^{ss} = \frac{Q}{V_1 \cdot k_{el}} \qquad [19]$$

A high steady state concentration will result from a high rate of infusion (Q) and from either a small volume of the central compartment (V_1) or a slow elimination constant (k_{el}).[3]

It should be noted that although the *magnitude* of the steady state plasma concentration depends on the infusion rate, the rate of drug elimination, and the distribution volume, the *rate* at which the steady state is achieved depends only on the rate of drug elimination from plasma (α and β). In practical terms, since α is so much greater than β for most drugs, attainment of a steady state during a constant IV infusion is essentially dependent on β alone, and it will be almost 97% complete in a period of 5 × $t_{1/2\beta}$. In order to achieve a given plasma concentration more quickly, an initial bolus dose or an initially more rapid rate of infusion can be administered followed by the infusion rate calculated to provide a given plasma concentration. These relationships are illustrated graphically in fig 10. An excellent example of the clinical application of constant IV infusion is provided by lidocaine in the therapy of cardiac dysrhythmias.[15]

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Clinical Reports

Plasma Lidocaine Concentrations Following Subcutaneous or Submucosal Epinephrine-Lidocaine Injection

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The addition of lidocaine to epinephrine injected subcutaneously or submucosally to achieve local hemostasis could decrease the arrhythmogenic potential of epinephrine following its absorption into the vascular system. The addition of lidocaine to epinephrine, for example, has been shown to increase the maximum safe dose of epinephrine that may be administered during halothane anesthesia,[1] presumably because of the antiarrhythmic effects of lidocaine which has been absorbed. Data on blood levels of lidocaine following its injection in solutions also containing epinephrine have not, however, been reported. The purpose of the present study was to provide such data following the subcutaneous or submucosal injection of 1:200,000 (5 μg/ml) epinephrine combined with 0.5% (5 mg/ml) lidocaine. The data obtained also provide quantitation for the first time of blood levels of lidocaine achieved when injected by technics that enjoy wide clinical popularity, namely, subcutaneous or submucosal injection of epinephrine-lidocaine solutions in neurosurgery and otolaryngology.

METHODS

Twelve adult patients scheduled for elective frontal or temporal craniotomy (6 patients) or transphenoidal hypophysectomy (6 patients) were studied. Chloroprocaine was used to provide local anesthesia for placement of intravenous and radial arterial catheters prior to induction of anesthesia. Blood pressure and ECG (lead 2) were continuously recorded. Anesthetic induction was with thiamylal (4 to 6 mg/kg) plus pancuronium (0.1 mg/kg) to facilitate tracheal intubation. Maintenance was with 60% N_2O and 1.0 to 1.5% inspired enflurane in O_2.

About 30 minutes after induction of anesthesia, freshly prepared 1:200,000 epinephrine in 0.5% lidocaine was injected by the surgeon into the scalp subcutaneously (40 to 60 ml over 30 to 60 seconds) or into the oral and nasal submucosa (15 to 20 ml over 90 to 180 seconds). The volume administered was determined by the surgeon. Arterial blood samples for determination of plasma lidocaine concentrations (exclusive of lidocaine metabolites)[2] were obtained immediately before injection and 1, 3, 5, 10, and 30 minutes after completion of the injection.

RESULTS

Plasma lidocaine concentrations are summarized in the table. Craniotomy (subcutaneous injection) and transphenoidal hypophysectomy (submucosal injection) patients are considered separately since the dose of epinephrine-lidocaine differed in the 2 groups. The highest lidocaine blood levels in the 2 groups (1.7 μg/ml and 1.3 μg/ml) occurred in the only 2 patients in whom systolic blood pressure increased significantly (50 torr and 40 torr, respectively). Ventricular irritability was not observed in any patient. Mean plasma lidocaine concentrations (exclusive of the 1.7 μg/ml and 1.3

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TABLE
Plasma (Arterial) Lidocaine (μg/ml)

Injection site	Control	Minutes after lidocaine-epinephrine injection 1	3	5	10	30	Patient weight (kg)	Volume epinephrine lidocaine (ml)	Epinephrine (μg/kg)	Lidocaine (mg/kg)
Subcutaneous (craniotomy)										
Patient 1	0.1	0.3	0.3	0.3	0.3	0.2	69	20	1.5	1.5
2	0.1	0.2	0.4	0.5	0.2	0.1	58	40	3.4	3.4
3	0	0.2	0.4	0.5	0.2	0.1	125	60	2.4	2.4
4	0	0.3	0.7	0.4	0.3	0	74	40	2.7	2.7
5	0	0.1	0.2	0.5	0.3	0.2	82	40	2.4	2.4
6	0	1.7*	1.0	0.8	0.5	0.1	65	40	3.1	3.1
Mean		0.22	0.50	0.50	0.30	0.12	79	40	2.9	2.9
SE		0.04	0.09	0.05	0.04	0.03	12	6	0.3	0.3
Submucosal (transphenoidal hypophysectomy										
Patient 1	0	0.4	0.5	0.4	0.3	0.2	74	17	1.1	1.1
2	0.1	0.7	0.6	0.8	0.6	0.5	88	20	1.1	1.1
3	0	0.6	0.5	0.5	0.4	0.4	70	16	1.1	1.1
4	0	0.6	0.6	0.9	0.7	0.4	82	15	0.9	0.9
5	0	0.5	0.7	0.8	0.5	0.3	96	15	0.8	0.8
6	0	1.3*	0.8	0.5	0.5	0.5	50	17	1.7	1.7
Mean		0.56†	0.65	0.64	0.50†	0.38†	77	16.7†	1.1†	1.1†
SE		0.05	0.04	0.05	0.06	0.05	6	0.9	0.06	0.06

*Not used in calculation of mean lidocaine concentration
†$p<0.05$ submucosal vs subcutaneous

μg/ml values) were less after subcutaneous than after submucosal injection despite a larger dose administered to the former group. Maximum mean (± SE) lidocaine concentrations of 0.50 ± 0.09 and 0.64 ± 0.05 μg/ml occurred 3 to 5 minutes after subcutaneous or submucosal injection.

DISCUSSION

Plasma lidocaine elevations following subcutaneous or submucosal lidocaine injection with epinephrine were minimal. This is not surprising since vasoconstriction produced by epinephrine would limit lidocaine absorption. Whether the lidocaine blood levels achieved in this study would prevent ventricular irritability produced by simultaneous systemic epinephrine absorption cannot be answered. Lidocaine blood levels ranging from 0.6 to 2.0 μg/ml have been reported as concentrations necessary to treat or prevent ventricular irritability after myocardial infarction.[3] However, lidocaine blood levels necessary to protect against epinephrine-induced ventricular irritability in a well-oxygenated heart during anesthesia are not known. It is conceivable that protective levels would be less than those required after myocardial infarction.

Evidence that systemic lidocaine absorption after simultaneous submucosal injection with epinephrine protects against ventricular irritability was suggested by a previous report demonstrating that the safe submucosal dose of epinephrine was nearly doubled when epinephrine was simultaneously injected with lidocaine.[1] Although blood levels were not measured in this study,[1] it is likely they exceeded those observed in our patients since the amounts of epinephrine and lidocaine employed were approximately twice the amounts we administered during submucosal injection. Indeed, amounts of the epinephrine-lidocaine injected in our study were minimal. However, the amounts we administered represent the concentration and volume routinely used when the two drugs are injected together under most clinical circumstances.

It seems likely that systemic absorption of epinephrine and lidocaine would occur concomitantly. Therefore, lidocaine blood levels and any protective effect from the local anesthetic would likely be greatest

when epinephrine absorption was also increased. Support for this is provided by the 2 patients in the present study who manifested systemic epinephrine effects (elevated systolic blood pressure) associated with the highest lidocaine blood levels.

Lidocaine blood levels did not correlate with the volume and dose of epinephrine-lidocaine administered. Blood levels of lidocaine were lower after subcutaneous than they were after submucosal administration even though larger doses were administered subcutaneously. This implies greater vascularity and, therefore, greater systemic absorption from the oral and nasal submucosal injection sites. Another factor involved in determining blood levels of lidocaine may be loss of epinephrine-lidocaine solution during surgical incision. Although a subjective observation, it was noted that more clear fluid appeared to escape following incision into the scalp than following incision into nasal and oral submucosal tisue. Conceivably, this may have decreased the amount of drug available for absorption at later measurement times (5 minutes or more after parenteral injection).

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Plasma Pseudocholinesterase Deficiency Associated with Diethylstilbestrol Therapy

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NUMEROUS drugs can cause plasma pseudocholinesterase (PCHE) deficiency, including echothiophate eye drops,[1] other organophosphates,[2] alkylating agents,[3-5] the MAO inhibitor phenelzine,[6] and oral contraceptive agents.[7,8] Hemodialysis,[9] liver disease,[10,11] and pregnancy[12-14] are also cited as causes of depressed PCHE levels. We recently cared for a patient in whom acquired PCHE deficiency appeared to be related to diethylstilbestrol (DES) therapy. Because of the clinical implications, and because this has not been reported previously, this case is presented.

CASE REPORT

A 78-year-old white male with carcinoma of the prostate metastatic to bone was scheduled for transurethral resection of the prostate.

Past medical history revealed colon resection for cancer in 1970 and a bilateral orchiectomy in September 1976.

During the present admission (June 1977) the patient experienced intermittent fever and shaking chills and was thought to be bacteremic. He was treated with gentamicin 55 mg IV q8h, ampicillin 1.5 g IV q6h, acetaminophen with codeine for pain, and flurazepam as a sleeping medication. Additionally, the patient was receiving diethylstilbestrol (DES) 1 mg orally 3 times a day, which he had been taking for 2 months.

Physical examination revealed an alert and oriented male who complained of inter-

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mittent chills. Height was 173 cm and weight was 61 kg. Vital signs were within normal limits. Relevant laboratory studies prior to anesthesia and surgery revealed hemoglobin 11.9 g/dl, blood urea nitrogen 25 mg/dl, and creatinine 1.4 mg/dl. Electrolytes, platelets, prothrombin time, partial thromboplastin time, and lactic dehydrogenase were normal. The serum glutamic-oxaloacetic transaminase was 93 (8 to 30, normal) and total alkaline phosphatase was 912 (45 to 110, normal) with heat stable (liver) fraction 300. Serum albumin and globulin were 3.0 and 4.8 g/dl, respectively.

Without premedication, anesthesia was induced by mask using halothane up to 2.5%, N_2O 3 L/min, and O_2 2 L/min. Following d-tubocurarine 3 mg IV, succinylcholine (100 mg) was given. Two attempts at intubation were required because of difficulty in exposing the larynx, and the patient received an additional 40 mg of succinylcholine. No other muscle relaxants were used during the case. With the patient in lithotomy and Trendelenburg position, ventilation was controlled. When the patient was returned to the supine position, 35 minutes after intubation, spontaneous ventilation was inadequate, with a measured tidal volume of less than 100 ml. A peripheral nerve stimulator revealed a faint twitch response. No posttetanic facilitation or fade was noted. Ventilation was controlled throughout the remainder of the procedure and continued with the aid of a ventilator in the recovery room. The patient was awake at the end of the procedure, as demonstrated by weak attempts to respond to commands designed to test hand grip and head lift. There was a gradual return of strength and respiratory effort, and 3 hours and 10 minutes after the administration of the succinylcholine, the patient was extubated. Mental status was normal following extubation, and the patient remembered being previously awake but profoundly weak.

Plasma pseudocholinesterase (PCHE) level in blood drawn in the recovery room was 1.3 IU per litre (7 to 19, normal), using the Dupont Automatic Clinical Analyzer technic.[15] This technic is a colorimetric assay at 600 nm, employing butyrylthiocholine as substrate, and the subsequent reduction of dichlorindophenol by thiocholine as the indicator reaction. The next day plasma PCHE was 1.7 IU per litre. A sample of serum was sent to Smith-Kline Laboratories, Los Angeles, and, using a colorimetric assay at 412 nm with butyrylthiocholine as substrate and dithiobisnitrobenzoic acid as indicator, the PCHE level was 0.3 units/ml (2.5 to 9.5 units/ml, normal). Dibucaine and fluoride numbers obtained by Smith-Kline were 100 and 96, respectively, demonstrating qualitatively normal enzyme and excluding known genetically determined variants. On July 1, 1977, DES was discontinued, and dexamethasone 1 mg orally once a day was begun. On October 12, 1977, PCHE was 4.6 IU per litre (7 to 19, normal). Review of the patient's previous medical records revealed that he had been given succinylcholine on 2 previous occasions with apnea of normal duration (see table).

DISCUSSION

Several studies show that both endogenous and exogenous estrogens depress hepatic synthesis or release of plasma PCHE, re-

TABLE
Summary of Laboratory and Clinical Data

Date	Procedure	Succinylcholine (mg)	Response to succinylcholine	PCHE* (7-19 IU/L)	Albumin (3-5 g/dl)†	Prothrombin time
1/15/70	A-P resection	160	Normal	...	3.3	Normal
5/9/75	Cystoscopy Stone manipulation	100	Normal	...	...	Normal
9/76	Bilateral orchiectomy	...	...	...	...	...
4/25/77	DES started	...	...	...	...	...
6/18/77	Cystoscopy TURP	140	Prolonged	1.3	3.0	Normal
7/11/77	DES discontinued	...	...	...	...	...
10/12/77	Off DES 3 months	...	...	4.6	3.8	Normal

*Plasma pseudocholinesterase, with normal range in International Units per litre

†Normal range in grams/decilitre

sulting in depressed plasma PCHE levels.[7,8,12,16,17] Men in the first 6 decades of life have higher plasma PCHE levels than do women, while after 60 the intersex difference in PCHE levels disappears.[8] Women not taking oral contraceptives have higher levels of plasma PCHE than do women taking such drugs.[8] During pregnancy, women experience a gradual decline in PCHE levels. This decline begins in about the 10th week of gestation with the lowest levels being reached 3 days postpartum, at which time the PCHE level averages 32.3% lower than nonpregnant values.[12-14]

The effect of the estrogen DES upon plasma levels of PCHE has not been studied in either men or women. However, in vitro, DES, along with a large number of other steroids, has been shown to have no direct inhibitory effect upon PCHE activity.[16]

There is no evidence that gentamycin, ampicillin, acetaminophen, codeine, or flurazepam causes plasma PCHE deficiency. Liver disease, a recognized cause of plasma PCHE deficiency[10,11] was present in our patient. However, it is doubtful that this factor alone accounted for the low PCHE in our patient. Plasma PCHE, albumin, and prothrombin time are all affected together in liver disease; an extreme derangement in one is associated with more or less equal derangements in the others. If liver disease alone were to account for our patient's extremely low plasma PCHE level, one would expect low albumin levels, in the range of 1.5 to 2 g/dl.[10] Jorge and Sanchez[11] found that all their patients with liver disease with a plasma PCHE level below 70% of the lower limit of normal had either a low albumin or a prolonged prothrombin time. Additionally, all patients with a PCHE level less than 53% of the lower limit of normal were in hepatic coma. Data we have gathered corroborate this relationship among PCHE, albumin, and mental status. Our patient had a plasma PCHE level 19% of the lower limit of normal, yet albumin and prothrombin time were both within the normal range, and he was certainly not encephalopathic. This suggests that some factor selectively depressing PCHE levels was superimposed on minimal generalized liver dysfunction.

We speculate that the DES administered to this patient, perhaps acting in concert with hormonal effects due to orchiectomy, and occurring against a background of mild liver disease, caused severe depression of plasma PCHE levels that resulted in prolonged ventilatory inadequacy following succinylcholine. Other patients on DES but without underlying liver dysfunction might show less severe depression of PCHE levels, similar to that which occurs in pregnant women or women taking birth control pills. Males with metastatic cancer of the prostate and concomitant mild liver disease may be particularly sensitive to further stress imposed upon the liver in the form of DES and possibly other estrogens. With the administration of estrogens, PCHE synthesis may be reduced, and PCHE may fall to such low levels that these patients have prolonged paralysis following administration of succinylcholine.

In summary, a case is reported in which diethylstilbestrol therapy of metastatic prostate cancer was associated with plasma pseudocholinesterase deficiency and prolonged ventilatory inadequacy following succinylcholine.

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The Mobile Respiratory Assistor: Evaluation of a New Ventilator for Neonatal Transport

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THE creation of specialized centers for the care of critically ill neonates, many of them suffering from cardiorespiratory failure, has raised problems in the transportation and stabilization of these patients to and from the referring institution.[1-3]

Although a wide range of commercial ventilators are capable of supporting infants in such transport situations, these units are expensive, often complex and fragile, and many require sources of electricity.[4,5] Furthermore, because of the logistical problem of equipping many ambulances both at referring and receiving hospitals with these pieces of equipment, we thought it desirable to develop a simple, inexpensive, and sturdy instrument that could be utilized by members of the transport team. Such a unit was devised at our institution at a time when more sophisticated commercial ventilators were unavailable to us (for fiscal constraints) and is called the Mobile Respiratory Assistor (MRA).

METHODS AND MATERIALS

The MRA is a portable unit, measuring 8 inches by 9 inches and weighing 2 pounds (fig 1). It is inexpensive and can easily be assembled from equipment normally available in a respiratory therapy department.

The MRA is powered by a standard gas tank or tanks at 50 psi pressure. It is manually controlled by the operator, and inspiratory pressures are delivered by digitally occluding the exhalation valve (Air Shield 24-600-70). Pressures delivered to the patient are measured on a manometer (Emerson) in series with the delivery system. A CPAP manometer/relief valve module (Healthdyne 32000) permits regulation of maximum inspiratory pressure (pop-off). This ventilator functions essentially as a constant-flow, time-cycled, pressure-limited respirator. Positive end-expiratory pressure (PEEP) can be added by adjusting the Air Shield exhalation valve on the expiratory limb of the delivery system. Manual control

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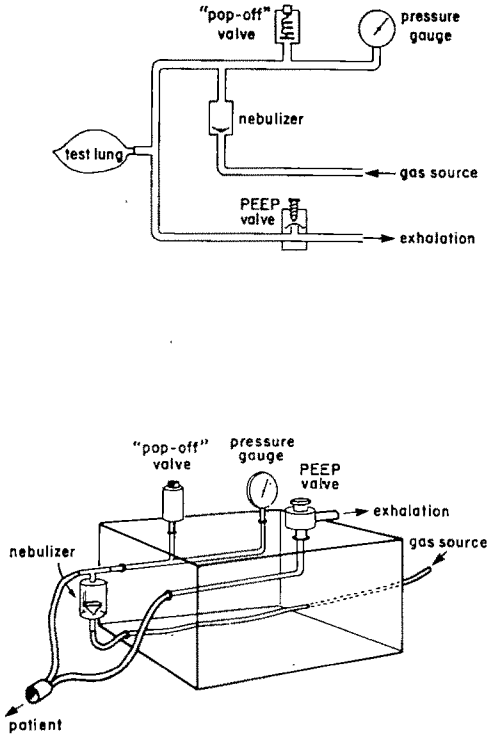


FIG 1. Schematic representation of the Mobile Respiratory Assistor (MRA)

of this respirator permits the operator to deliver either controlled ventilation or intermittent ventilation similar in concept to intermittent mandatory ventilation (IMV).[6] It can also serve to maintain continuous positive airway pressure (CPAP) in a spontaneously breathing patient (see table 1 for operating instructions).

Oxygen and/or air can be used to power the ventilator, and a blender in series with the gas source(s) can adjust the fractional inspired O_2 concentration (F_IO_2) to desired levels. Gas is humidified through a Hudson nebulizer (10 cc of H_2O will humidify the gas delivered for 1 hour).

TABLE 1
Instructions for Operation
(Neonatal Transport Situation)

1. Set gas flow rate at 7 L/min.
2. Fill Hudson nebulizer with 10 cc of water.
3. Adjust pressure release valve (turn clockwise) to desired pop-off. (Simulator or test balloon can be used to adjust pressure initially.)
4. Set PEEP pressure by observing baseline pressure on manometer (initially may be done on test model).
5. Ventilation is accomplished by intermittently occluding the opening of the exhalation valve at the desired rate.
6. CPAP is delivered by maintaining the stem opening of the PEEP adaptor open.

The inspiratory limb of the system is connected to an endotracheal or tracheostomy tube, but can also function when attached to a face mask or nasal prongs. It can easily be used for infants being transported in incubators because of its simplicity and compactness.

In practice, delivered tidal volume (TV) is estimated by using a test lung (rubber balloon) as illustrated in fig 1. Auscultation, chest-wall expansion, and peak airway pressures are monitored once controlled ventilation is instituted.

For transport situations which involved neonates with respiratory distress or prematurity, we have found that gas at an appropriate F_IO_2 delivered at 7 L/min with a pop-off setting of 30 cm H_2O is a good starting point for adjusting ventilator settings.

The ventilator was evaluated using an Infant Lung Airway Simulator (Bourns, Inc., Model LS130). The MRA was attached to the test lung via a 15-mm (diameter) connection. This simulates the patient's "proximal airway," and pressure is monitored at this point.

Flow from the MRA continues from this proximal airway to the endotracheal tube port of the lung airway simulator. A 2.5-mm (Portex) endotracheal tube was used to connect the proximal to the distal port. From this point, flow in the simulator is channeled into selective resistances and compliances. "Lung" pressure is measured at this level. Both proximal airway and lung pressures were displayed on a dual trace oscilloscope, and a permanent record was made on a 2-channel (Hewlett Packard 7402A) recorder.

Inspiratory and expiratory times, proximal airway and lung pressures, and PEEP were read directly from the tracings (fig 2). The total respiratory cycle was calculated as the sum of inspiratory and expiratory times; the respiratory rate was calculated by dividing 60 seconds/minute by the total respiratory cycle. Tidal volume was calculated by multiplying the simulated compliance by the driving pressure (= peak lung pressure minus PEEP). Measurements were averaged over 10 simulated respiratory cycles.

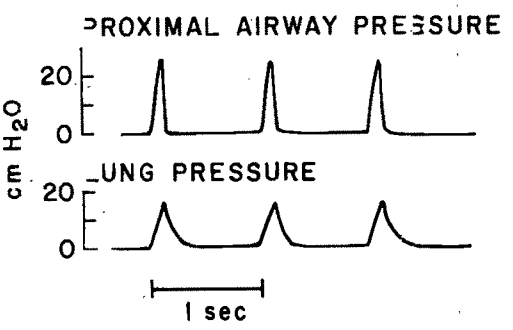


FIG 2. Proximal airway and lung pressure recorded by the Infant Lung Airway Simulator (Bourns LS130) while testing the MRA. Simulator settings:

MRA settings:
Gas flow = 7 L/min
PEEP = 0 cm H_2O

Compliance = 1 cc/cm H_2O
Resistance = 200 cm H_2O/L/sec

RESULTS

The MRA was tested under a number of simulated conditions. Three sets of compliance-resistance settings were used to illustrate different clinical situations (table 2). Flow rates of 7 and 12 L/min of O_2 were used at these settings to deliver gas to the ventilator. PEEP was set at 0 and 6 cm H_2O. The pop-off was maintained at 30 cm H_2O. Results are shown in table 2. The ventilator delivered a narrow range of TV at each compliance-resistance setting, with the volumes being higher at the high flow rates of gas delivery. In all instances, the I:E ratio was maintained at less than 1:2 with longer expiratory times being achieved at the 12 L/min flow. At high respiratory rates I:E increased but no air trapping occurred, as documented by the simulator. The addition of small amounts of PEEP (6 cm H_2O) did not in most instances alter either TV or the I:E ratio when abnormal mechanical lung properties were present. When compliance and resistance were relatively normal, changes in flow and PEEP did result in significant alterations of tidal volume (table 2).

The internal compliance of the ventilator was measured by occluding the expiratory port, closing the pop-off, and injecting 2.5, 5, 7.5, and 10 cc of air into the ventilator. The compliance was thus found to be 0.3 cc/cm H_2O.

This implies that when the ventilator is pressure limited at 30 cm H_2O without PEEP, 10 cc of gas are compressed within the ventilator and not delivered to the neonate.

DISCUSSION

In the two years since its introduction, the MRA has been used extensively, initially in situations where other ventilators (eg, Cavitron) were not available. Currently, it is used as a backup of the transport equipment for premature infants and infants transported with respiratory disorders.

Clinical experience with this unit indicates that it offers a practical alternative in situations where more sophisticated ventilatory devices are not available or are in use for concurrent emergency (eg, transport of multiple-birth infants with respiratory failure).

Testing of the MRA by the lung simulator demonstrates that this simple ventilator can be adjusted to deliver a stable TV under different pressure restraints (eg, PEEP) and respiratory rates without gas trapping. Peak pressures can easily be maintained in a safe range.

The design of the MRA permits it to be used for controlled ventilation as well as for delivering an appropriate F_IO_2 to a spontaneously breathing infant. PEEP or CPAP and the maximum airway pressure are easily adjusted. Rate and tidal volume are controlled by the operator. The MRA is readily assembled and taken apart for easy maintenance and cleaning. Finger fatigue has not been a problem.

The MRA offers a practical backup system to the use of commercial ventilators in transport situations. It may also prove useful in institutions where economic or other constraints limit the number of available infant ventilators.

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TABLE 2
Tidal Volume (TV) and Inspiratory to Expiratory Time Ratio (IE) of the MRA Demonstrated by the Infant Lung Simulator at Different MRA Settings

		MRA setting							
	Flow (L/min)	7	7	7	7	12	12	12	12
	Respiratory rate (breaths/min)	20	20	40	40	20	20	40	40
	PEEP (cm H_2O)	0	6	0	6	0	6	0	6
Lung simulator setting	TV (ml)	34 ± 5.0†	31 ± 1.8	39 ± 2	31 ± 2.3	38 ± 3.3	45 ± 4	48.2 ± 3.3	42 ± 3.3
C_5R_{50}*	I:E	1:7.4	1:7	1:2.6	1:4.2	1:7.1	1:7.2	1:3	1:3
C_2R_{100}	TV	26.8 ± 1.7	26.8 ± 1.5	25.6 ± 0.9	29.2 ± 0.9	34.4 ± 2.3	31.2 ± 1.3	30.0 ± 0.9	31.2 ± 1.9
	I:E	1:6.1	1:6	1:3	1:2.3	1:6.1	1:7	1:3	1:3
C_1R_{200}	TV	18.2 ± 0.7	22.4 ± 0.8	21.8 ± 1.1	23 ± 1.0	23.4 ± 1.3	21.6 ± 1.1	21.8 ± 0.8	21.4 ± 1.2
	I:E	1:8	1:5.7	1:2.3	1:2.5	1:7.4	1:6.4	1:2.1	1:2.7

*C = Compliance, R = Resistance

†Mean ± SEM

Subscripts represent simulator settings, with C in ml/cm H_2O and R in cm H_2O/L/sec.

Adult Radial Artery Puncture Simulator

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ARTERIAL puncture and cannulation are procedures now commonly practiced in the management of critically ill patients and patients undergoing extensive surgery. These technics provide a means for monitoring arterial blood gases and pH, provide accurate measurement of arterial blood pressure, and greatly facilitate in quantitation of hemodynamic responses. The increasing use of these procedures has resulted in a greater need for the teaching of technics of arterial puncture and arterial cannulation to medical students, resident house staff, and nursing and respiratory therapy personnel. To meet this need an adult radial arterial puncture simulator has been developed.

The simulator is a soft plastic model which depicts the ideal position of the hand and wrist in dorsiflexion (fig 1). The molding and casting technics used in the fabrication of the simulator are, for the most part, described in the literature supplied by the manufacturers of the materials. The sequence of construction begins with the use of Dow Corning 3110 RTV silicone rubber to make a mold of an arm and hand. Flesh-colored liquid latex rubber is then painted on the inside of the mold and allowed to dry. This latex will become the skin. Polyurethane foam is poured into the mold and allowed to expand and cure. The foam and latex casting is removed from the mold and a block of foam is cut from casting to allow positioning of internal parts. The internal parts consist of a plastic armature and rubber tubing. The armature is molded from clay or wax. Molds of the armature are made from RTV silicone rubber and casting is done with self-curing plastic.

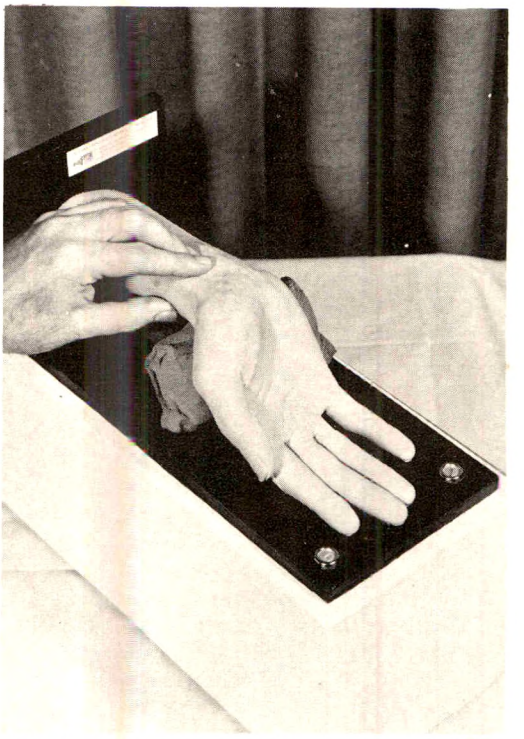


FIG 1. Pulse palpation with simulator, depicting the ideal dorsiflex position of wrist and hand

A schematic representation of the simulator is depicted in fig 2. The tactile pulse is achieved with a mechanical device which

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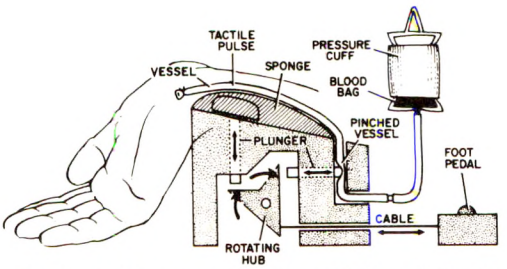


FIG 2. A diagrammatic representation of the internal parts of the simulator

taps the vessel from below at the wrist area. A second contact is made simultaneously but proximal to the first and is firm enough to pinch the vessel and cause an intermittent surge of fluid pressure within the vessel. There is no actual fluid flow until the vessel is punctured and then the fluid spurts from the vessel in a pulsatile manner. Fluid pressure is achieved by an inflatable pressure cuff on a blood reservoir bag. A foot pedal controls the pulse and can be operated by student or instructor. The lifelike skin texture and color permit a realistic demonstration of skin preparation of the puncture site with an appropriate antiseptic agent.

After locating the point of strongest pulsation along the vessel's course, the puncture can be made with a syringe needle or with a unit consisting of a plastic cannula over a needle. The simulated skin and vessels may be punctured 300 to 500 times before they must be replaced. The simulated blood solution is "self-coagulating" due to the addition of radiator leak stop. This prevents leakage from the vessel and permits the intraluminal pressure to be maintained in a range of 100 to 150 torr. Upon penetration of the lumen of the artery with a 20-gauge or smaller needle, the plunger of the syringe is forced back by the intraluminal pressure in a distinct pulselike movement and the barrel fills with the bright red solution, closely simulating the color and consistency of oxygenated arterial blood (fig 3). Since the glass syringe has a much lower coefficient of friction compared to plastic syringes, the pressure of the artery fills the syringe without aspiration.

The model allows a skin nick to be made with an 18-gauge needle. Advancement of a 20-gauge catheter through the nick along the course of the artery is easily accomplished. When puncture of the artery occurs, blood rapidly appears in the needle hub. The cannula is advanced into the lumen of the vessel, and when the needle is withdrawn a brisk pulsatile flow of blood issues through the hub of the catheter. Once the catheter has been advanced fully, it may be attached to a pressure manometer and a means of securely taping the catheter in place may be demonstrated and practiced with the model. Various procedures for the intermittent or continuous infusion of a heparinized solution to maintain catheter patency can also be easily demonstrated with the use of the simulator.

The adult radial artery puncture simulator is a manually functioning model providing a realistic-appearing arm with bony and tendinous landmarks, a palpable pulse, and a pulsatile blood flow. With the simulator, the basic concepts and technics of intermittent arterial pressure and arterial cannulation have been easily demonstrated to and practiced by numerous medical and paramedical personnel at our institution prior to their attempting to perform these procedures in the clinical situation.

At the present time the simulator is not commercially available. We are, however, able to provide a limited number of simulators upon special order. Further information can be obtained by writing Craig G. Gosling at the address listed on the first page of this article.



FIG 3. With arterial puncture, intraluminal pressure of model forces a simulated blood solution into the syringe

A Rapid, Simple Technic for Changing Endotracheal Tubes

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In the critically ill, intensive care unit patient, replacement of endotracheal tubes may be technically difficult or traumatic and may be associated with an increase in morbidity and/or mortality. A rapid, easy technic for changing endotracheal tubes would be a welcome addition to the clinicians' armamentarium.

This paper describes a quick, simple technic for changing nasotracheal or orotracheal tubes (henceforth termed endotracheal tubes, or, simply, tubes) without the need for a laryngoscope or bronchoscope.

DESCRIPTION

The technic to be described (which is similar to that reported by Finucane and Kupshik[1]) was first performed an average of 10 times in 8 healthy dogs and, once proven safe and effective, was used in 51 endotracheal tube changes in 48 patients in our critical care units over a 6-month period. The tube changer (guide) (fig 1) is 28 inches long and made of polyethylene tubing with an open central lumen. These guides can be made from commercially available ¼-inch OD tubing for endotracheal tube sizes 7, 7½, and 8 mm. For tube sizes 8½ mm ID and larger, ⅜-inch tubing is recommended. For endotracheal tube sizes 5½, 6, and 6½ mm, ⅛-inch OD tubing is used. The precise depth the sterile guide is advanced inside the endotracheal tube is determined by the ring (fig 1 and 2) on the guide shaft. The short distance between the two rings provides ample room for grasping the guide to immobilize it while changing the endotracheal tube. Distally, from each ring there are 1-cm graduations (not shown in illustration) which are used to maintain the precise depth of insertion during tube changes. Either end of the guide may be directed into the endotracheal tube. Insertion-distance corrections must be made when the proximal end of the endotracheal tube has been cut off.

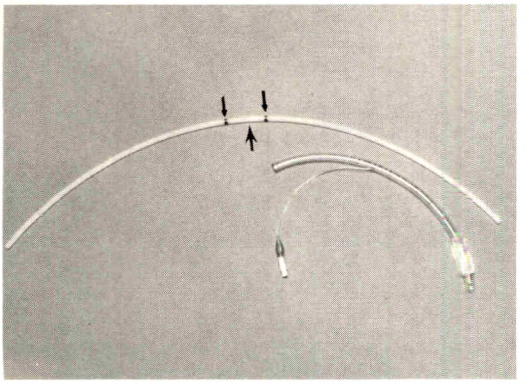


FIG 1

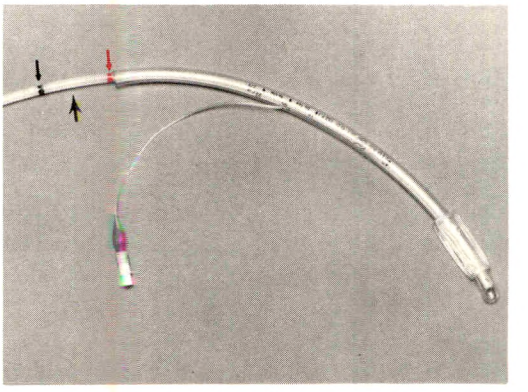


FIG 2

METHODS

Specifically, the procedure is as follows: Once the appropriate-size guide is select-

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On request, the authors will provide the name and address of the company that has made these tube changers commercially available.

ed, the replacement endotracheal tube cuff is deflated, lubricated, and the tube placed on a sterile wrapper. The 15-mm adaptor is removed from the patient's existing endotracheal tube, after which the guide is inserted intralumenally to the first ring, thus assuring the guide's tip is adjacent to the endotracheal tube's distal bevel. If the endotracheal tube has been shortened, the guide must be advanced to a corresponding lesser depth. Once the guide is at the proper depth, the tube cuff is deflated and the endotracheal tube pulled back and removed. The guide's position is stabilized by grasping the proximal end nearest the patient. The replacement tube is then passed over the guide and repositioned until its distal end is at the guide ring. The guide's position must be stabilized during this maneuver. The guide is then removed, the endotracheal tube reattached to the appropriate 15-mm adaptor, and the cuff inflated to the proper seal.

If the patient is in need of supplemental O_2 during this procedure, it can be supplied via a small catheter which may be directed through the guide lumen. Since the endotracheal tube change takes less than 1½ minutes, there is usually no need for supplemental O_2.

DISCUSSION

The technic described herein can be easily performed by even relatively inexperienced persons. We have taught house staff, medical students, and paramedical personnel to use this procedure in less than 5 minutes. The time for tube changes normally ranges from 30 seconds to 1½ minutes.

As with any other procedure, certain precautions must be observed during endotracheal tube changes. In order to avoid tracheal mucosal damage, the guide's tip should remain proximal to the endotracheal tube distal bevel. To minimize any potential damage, the end of the guide is highly polished and very smooth. Nonetheless, it is suggested that the operator not push the guide tip past the tip of the endotracheal tube. In order to prevent this occurrence, the guide is advanced only to the first ring (fig 1 and 2). As mentioned under Methods, corrections for shorter endotracheal tubes must be taken into allowance. Advancing the guide to the first ring through an orotracheal tube that has been shortened will cause the guide to protrude that distance beyond the bevel with the potential for trachael mucosal trauma.

Although stabilization of the guide's position will help assure proper depth of insertion of the new tube, radiographic verification of correct endotracheal tube depth is recommended.

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A Modified Dawkins Epidural Indicator: A Useful Teaching Aid

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THE successful administration of epidural analgesia depends on the ability of the anesthesiologist to master the art of identifying the epidural space. Critical evaluation of various devices and technics used for identification of the epidural space are found in the reviews by Lund[1] and Dawkins.[2] In general, these devices depend on identification of either negative pressure within the epidural space or loss of resistance to the injection of air or liquid when the tip of the needle enters the space.

The Dawkins epidural indicator[2] consists of a vertical nylon tube of 3 mm in internal diameter. The tube is filled with saline or anesthetic solution and attached to the hub of the epidural needle. When the tip of the

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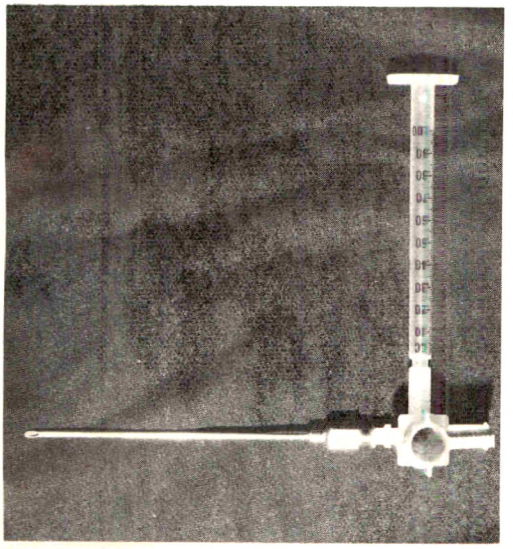


FIGURE. The device attached to the epidural needle in the functioning position

needle enters the space, movement of the meniscus is observed.

METHOD AND MATERIALS

A modified Dawkins epidural indicator may be assembled with inexpensive, disposable, sterile components found in any American hospital. It consists of the barrel of a standard tuberculin or 1-cc (long) insulin syringe which is attached to a 3-way plastic stopcock, which in turn is attached to the hub of the epidural needle so that the barrel is at right angles to the needle shaft in the vertical plane (fig). The total weight is 5.3 g. The device is operational when the barrel is filled with sterile saline. It is attached to the hub of the needle when the tip is close to the ligamentum flavum. The entire unit is advanced toward the dura while closely observing the meniscus. As the needle enters the epidural space downward, movement of the meniscus is seen. If inadvertent puncture of the dura should occur, upward movement of the meniscus is seen as the tube fills with cerebrospinal fluid. The subarachnoid position of the needle may be also confirmed by a Valsalva maneuver causing upward movement of the meniscus.

RESULTS

The device was used on 28 patients. It was observed that a consistent drop in the level of the meniscus occurred when the needle entered the epidural space. This change was variable, ranging from 2 mm to 1.4 cm.

When the needle was advanced to impinge on the dura an additional variable drop in the meniscus level of 2 to 8 mm was found in 16 patients. The dura was inadvertently punctured in 2 patients. This was immediately detected by observation of a slow persistent rise in the level of the meniscus. The response of the manometer was very sensitive and enabled even the inexperienced resident to accurately identify the epidural space.

DISCUSSION

The Dawkins indicator offers a reliable visual method of locating the epidural space. It depends on the combined forces of gravity and negative pressure in the epidural space. Obviously the force of gravity is constant; however, the negative pressure may vary from −0.25 mm to −12 mm Hg.[2] Should the needle point impinge on the dura, a cone of depression is formed resulting in an increase in negative pressure in about 42% of cases.[2] The rate of fall of the column of saline in the barrel of the tuberculin syringe depends on the gradient of this negative pressure. Dawkins found that a "movement of the meniscus will take place in 95% of cases." Consequently, he was convinced that "The method would therefore appear to be more sensitive than the feel of the thumb on the piston."[2]

There is no evidence that the modified Dawkins indicator changes the sensitivity of the original device. Although the bore of the syringe barrel is slightly larger than that of the original Dawkins device, it nevertheless functions well as a reservoir for the column of fluid. The additional weight of the fluid column increases the movement of the meniscus should the negative pressure in the epidural space be minimal. The 3-way stopcock serves as a convenient method of filling the barrel with fluid. In addition, it also is used as a handle, affording better control of the advancing epidural needle.

The graduated markings on the barrel facilitate accurate observation of very small movements of the meniscus. The small changes can be easily observed from a distance of 3 to 4 feet at any angle. Thus, the technic can be used to demonstrate a means for accurate identification of the epidural space to a group of 4 or 5 observers standing in different positions with reference to the back of the patient and the anesthesiologist,

an advantage in a training program. This situation contrasts with a demonstration of the hanging drop method of Gutierrez.[3] The shifting of the hanging drop is difficult to see at various angles and from any appreciable distance.

The availability of the components in sterilized packs is also an advantage. Since the device is disposable, the costly labor of repacking and autoclaving is avoided. It is estimated that the components cost less than a dollar.

It would be an advantage for the resident to become familiar with the Dawkins method in addition to the tactile or loss-of-resistance technics. In this way he may be able to make an intelligent choice of the method that can be managed with accuracy, efficiency, and ease.

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Multiform Ventricular Tachycardia Due to the Interaction of Aminophylline and Halothane

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SINCE halothane is a potent bronchodilator,[1] it is an acceptable choice, perhaps even the best choice for anesthetizing patients with asthma.[2] However, halothane "sensitizes" the heart to exogenous catecholamines.[3] The latter drugs are commonly used to treat asthma. Xanthines are effective bronchodilators because they produce beta-adrenergic stimulation in two ways. They cause release of norepinephrine[4,5] and they also inhibit breakdown of cyclic 3'5' AMP,[6] the mediator of many of the actions of beta-adrenergic agonists.[7] Therefore, the combined use of halothane and xanthines in asthmatic patients may lead to cardiac arrhythmias. We are unaware of published reports of adverse effects from this interaction. This dearth of reports may be due to lack of significant drug interaction despite the theoretical possibility or simply because the drug combination is usually avoided by most clinicians.

This report details two cases of multiform ventricular tachycardia we believe due to the interaction of halothane and aminophylline in asthmatic patients.

REPORT OF CASES

Patient 1 — A 65-kg, 57-year-old farm housewife was admitted for bronchoscopy and open lung biopsy of one of three right middle lobe pulmonary nodules 10 years after radical mastectomy for adenocarcinoma involving her right breast and at least one axillary lymph node. Tissue was need-

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ed for estrogen receptor binding assay to guide therapy for presumed metastatic breast carcinoma. Past medical history revealed episodic shortness of breath about every 6 months over the last 20 years. The episodes were characterized by wheezing, were often related to exposure to cats, dust, furnace cleaning, or horse riding, and were usually improved on leaving the farm or subcutaneous epinephrine administration in a local emergency room. She had never been hospitalized for asthma, nor did she have symptoms or signs suggestive of angina, myocardial ischemia, or congestive heart failure. Three times previously she was anesthetized; each time her anesthesiologist told her she "went too deep" with thiopental and advised her not to receive it again. She knew of no history of asthma during or following anesthesia.

Pulmonary function tests on admission revealed a decreased vital capacity (2.8 L predicted, 2.5 L actual), increased residual volume (1.7 L predicted, 2.8 L actual), and decreased FEV_1 (70% of actual vital capacity). These tests did not improve after inhalation of 0.5% isoproterenol. Nevertheless, an infusion of 40 mg/hr of aminophylline was begun. Five hours later, with the infusion still at 40 mg/hr, the preoperative evaluation was made by the anesthesiologist. Physical examination was unremarkable except for a right radical mastectomy scar. Her chest was clear. Blood pressure lying and standing was 130/80 torr, with a pulse rate of approximately 88. Jugular venous pressure (estimated by neck vein examination) was 4 cm H_2O. Laboratory data included a normal ECG, a hematocrit of 35.2%, normal electrolytes and blood urea nitrogen, an arterial Po_2 of 71 torr while breathing room air, with a Pco_2 of 36 torr and pH of 7.44.

The potential of an interaction between aminophylline and anesthetic agents was discussed with the pulmonary consultant, and it was agreed to stop the aminophylline infusion 2 hours prior to the patient's scheduled arrival in the operating room. In addition, the pulmonary consultant ordered a blood sample drawn for serum aminophylline concentration; after the blood was drawn (but before the result was available), he increased her aminophylline infusion to 55 mg/hr. Three hours prior to induction of anesthesia, the patient received 15 mg of diazepam orally. During placement of the IV and arterial lines, the patient stated that she had been awakened 4 hours previously by a left temporal headache which had only recently subsided. During continuous monitoring of ECG and direct arterial blood pressure, anesthesia was induced using a mask and 3 L/min of N_2O, 2 L/min of O_2 with gradually increasing concentrations of halothane. When the inspired halothane concentration reached 2%, ventilation was controlled. Her blood pressure remained 160/90 torr as it was on arrival in the operating room. Five minutes after induction at a time when the inspired halothane concentration had been 2.5% for approximately 1½ minutes, a multiform ventricular tachycardia developed with a rate of 160 to 170. Blood pressure fell to 110/60 torr. Her ventilation was controlled with 1.5% halothane and 98.5% O_2. We gave 100 mg of lidocaine IV and drew a sample of arterial blood. One and one-half minutes later, her rhythm returned to normal sinus rhythm and her blood pressure to 130/80. After 6-leads of her ECG were found to be unchanged from the corresponding 6-leads obtained preoperatively, endotracheal intubation was performed with the aid of 3 mg of d-tubocurarine and 90 mg of succinylcholine. Operation and subsequent hospital course were otherwise uneventful. Arterial gases at the start of the multiform ventricular tachycardia were Po_2 102 torr, Pco_2 27 torr, and pH 7.41. A 12-lead ECG in the recovery room was unchanged from all 12-leads obtained prior to anesthesia. Subsequently, the laboratory reported the preoperative plasma aminophylline level drawn while the patient was receiving 40 mg/hr of aminophylline to be 21 mg/L.

Patient 2—The second patient was a 54-year-old male 190 cm tall, weighing 99 kg, scheduled for rectal fistulectomy. The patient had taken 500 mg of aminophylline orally every 6 hours for several years for intermittent wheezing. Preoperative pulmonary function tests revealed a vital capacity of 3.8 L (5.7 predicted) with an FEV_1 of 2.0 L (53% of actual vital capacity). Chest examination revealed no wheezing. The patient adamantly refused regional anesthesia. Two hours prior to induction of anesthesia, the patient received 500 mg of aminophylline and 20 mg of diazepam orally.

With continuous ECG monitoring, anesthesia was induced using a mask with 3 L/min of N_2O, 2 L/min of O_2, and increasing concentrations of halothane. When the inspired halothane concentration reached 2%, ventilation was controlled. Blood pressure was 115/70 torr, reduced from 140/85

torr preoperatively. Five minutes after induction, with an inspired halothane concentration of 3% for 1 to 1½ minutes, a multiform ventricular tachycardia developed with a rate of 150/min. Blood pressure fell to 100/60 torr. Nitrous oxide was replaced with O_2, the inspired halothane concentration decreased to 1.5%, and 100 mg of lidocaine were given IV. Arterial blood was drawn for measurement of gas tensions. Approximately 1 minute later his rhythm converted to atrial fibrillation with a ventricular rate of 130 to 140/min. One minute later normal sinus rhythm returned. After a 12-lead ECG was shown to be unchanged from that obtained preoperatively, endotracheal intubation was performed with the aid of pancuronium and succinylcholine. Operation and subsequent hospital course were uneventful. Arterial gases during the episode of ventricular tachycardia were Po_2 398 torr, Pco_2 41 torr, pH 7.37. Electrocardiograms obtained in the recovery room and on the 3rd postoperative day were unchanged from the ECG obtained at the time of admission to the hospital.

DISCUSSION

Aminophylline has long been known to have the potential for production of fatal arrhythmias. In a retrospective analysis of cardiac arrests in the University of Southern California intensive care unit,[8] aminophylline was 60 times more "predisposed to cause" cardiac arrest than any other drug, including digoxin. In addition, aminophylline was "responsible for" 36% of cardiac arrests in that ICU not preceded by respiratory or metabolic acidosis.

Plasma theophylline levels of 5 mg/L are needed to reduce abnormal elevations of airway resistance. No further beneficial effects are obtained with levels greater than 20 mg/L. Instead, toxic effects start to appear.[9,10] Theophylline (aminophylline is a combination of 85% theophylline and 15% ethylenediamine) is largely metabolized by the liver, with less than 10% excreted unchanged in the urine. The average half-life is 4.4 ± 1.15 hours in adults with a clearance of 1.2 ml/min/kg.[9] Neither of our patients had significant liver disease or pulmonary edema, both of which can decrease the clearance of the drug, by one-half and one-third, respectively.[11] The second patient was a cigarette smoker; cigarette smokers clear aminophylline more rapidly than nonsmokers.[12] The first patient had a theophylline level of 21 mg/L when the infusion rate was 40 mg/hr. Her headache the morning of surgery may well have been a sign of toxicity. At that time she was receiving a 55 mg/hr infusion; her predicted theophylline level was thus 29 mg/L. Her ventricular tachycardia occurred 2 to 2.5 hours after stopping her 55 mg/hr aminophylline infusion. At that time her aminophylline level was probably at or above the upper limit of the therapeutic range.

The mechanism by which aminophylline produces its therapeutic and toxic effects remains unproven. Rall and West,[6] however, have shown that theophylline inhibits formation of phosphodiesterase. Phosphodiesterase catalyzes the breakdown of cyclic 3'5' AMP. Thus, inhibition of phosphodiesterase by theophylline increases the concentration of cyclic 3'5' AMP. Marcus et al[4] and Westfall and Flemming[5] have shown that at least 40% of the inotropic effects of aminophylline are due to its ability to directly release norepinephrine. Aminophylline infusion also increases urinary catecholamine excretion.[13] Experimentally, aminophylline decreases the threshold for ventricular fibrillation.[14]

Thus, since halothane is known to increase the arrhythmic potential of catecholamines, and since aminophylline is known to exert its effect by both the direct release of beta-adrenergic agonists and inhibition of breakdown of cyclic 3'5' AMP, a logical explanation for an interaction between these drugs exists. We believe these two cases of multiform ventricular tachycardia were due to the interaction of halothane and aminophylline. This interaction merits further study. In the meantime, we believe it is advisable to wait three half-lives after the last dose of aminophylline (approximately 13 hours in normal individuals) before using halothane to anesthetize an asthmatic patient. Another anesthetic that is a bronchodilator[1] but is less likely to predispose to catecholamine arrhythmias[15,16] such as enflurane might be an alternative in patients who must receive aminophylline prior to or during surgery.

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Epidural Anesthesia: 22-Gauge Needle

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THE introduction of long-acting local anesthetics has made the use of a single-dose epidural anesthetic a more feasible alternative to other forms of anesthesia for abdominal, perineal, and lower limb surgery. Most authors describe the use of 16-to-20-gauge needles for epidural anesthesia and do not mention smaller gauge needles.[1-6] Single-dose epidural anesthesia using a 22-gauge, 2.5-inch disposable needle has been used by McCaul for approximately 15 years at the Royal Women's Hospital in Melbourne,§ where one of the authors (M.J.D.) learned the technic. This paper describes our experience in teaching and introducing this technic at our institution.

METHOD

Single-dose epidural anesthesia using a 22-gauge, 2.5-inch disposable spinal needle

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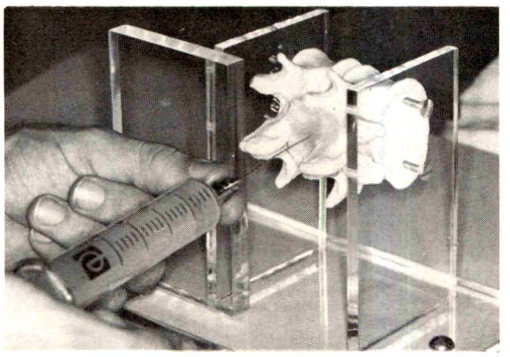


FIG.

was performed in 100 patients having a wide variety of abdominal, perineal, and lower extremity operations. Prior to using the method on patients, residents were taught the basic components of the technic on a model we designed. This model (fig) consisted of an acrylic frame which supported two lumbar vertebrae and a silicone material which was molded to fit between the two vertebrae to simulate the ligamentum flavum. When the loss-of-resistance test was applied to this model, the feel of the changes in resistance is similar to that felt in patients.

The success and complication rates in the first 100 single-dose epidural anesthetics performed with this technic were determined. Those patients in whom an inadvertent dural puncture occurred were followed to ascertain the frequency of headaches.

TECHNIC

The patients were positioned in the lateral position, although occasionally the sitting position was used. A disposable spinal anesthesia kit was used; a sterile 20-cc glass syringe, sterile local anesthetic for epidural injection, and a 22-gauge, 2.5-inch disposable spinal needle were added. This needle is 1 inch shorter than the commonly employed 3.5-inch spinal needle, and does not bend as readily.

After careful skin preparation and draping, the epidural space was identified using the loss-of-resistance technic. With the sharp fine-gauge needle, several points in technic should be stressed. First, the needle must be inserted into the midline so that the interspinous ligament and ligamentum flavum prevent air from escaping through the needle as pressure is applied to the barrel during advancement of the needle and attached air-filled syringe. Second, the hub of the needle should simply be supported by the finger and thumb of the left hand; this hand should not be used to advance the needle point. The point of the needle is advanced by constant, unremitting, gentle pressure with the palm or thumb of the right hand on the plunger of a 20-cc glass syringe well lubricated with local anesthetic and containing 5 cc of air. In most cases, as the needle point enters the epidural space the loss of resistance is readily felt, so that only 1 or 2 cc of air need be injected into the epidural space. The left hand holds the hub of the needle firmly as the syringe is disconnected and later reconnected to the needle after being filled with the local anesthetic to be injected. Needle movement after detecting the loss of resistance accounted for three dural punctures, so that firmly holding the needle hub cannot be overemphasized.

If no blood or cerebral spinal fluid is obtained after aspiration, a test dose can be given. Since local anesthetic may be injected into the subarachnoid space if the needle is accidently advanced during subsequent injection, we recommend that after the test dose is given aspiration should be repeated during subsequent injection of local anesthetic. We aspirate after each 5 cc of local anesthetic are injected.

Upon completion of the injection and removal of the needle, we observe the patient's vital signs at frequent intervals so that the onset of the uncommon complication of total spinal will be promptly recognized and treated.

RESULTS

Analysis of the first 100 single-dose epidurals is summarized in the table. There were 7 failures of the technic: in 2 patients no anesthesia was obtained; in 4 patients dural puncture was detected and 1 patient developed total spinal anesthesia. None of the patients who had inadvertent dural punctures developed headaches.

The total spinal anesthetic occurred in the 10th patient of our series when the technic was being performed for the first time by a resident. Intrathecal injection occurred despite a negative response to the test dose. This brought to our attention the importance of repeated aspiration and the needle hub fixation during injection of local anesthetic agent. The surgical procedure was completed uneventfully and the patient recovered without complications.

TABLE
Analysis of Epidural Blocks

Number of cases	100
Successful blocks	93
Performed by residents	88
Dural punctures	5
Post-lumbar puncture headaches	0
Total spinal	1

DISCUSSION

This technic has several advantages over those using larger gauge needles. First, it reduces patient morbidity in a teaching situation, because the problem of post-lumbar puncture headache following inadvertent dural puncture is significantly decreased. Second, the loss-of-resistance test can be performed prior to spinal anesthesia (and on a simple model, increasing the resident's skill with the technic). Finally, if the essential features of this method are adhered to, then this technic is safe, reliable, and effective.

Small-gauge needles for single-dose epidural anesthesia have not gained popularity because the loss of resistance upon entering the epidural space was not thought to be clear cut. In our first 100 epidural blocks, 93 were successful even though most (88) were performed by residents, indicating that the technic can be mastered quickly. The success rate is similar to that reported by others who use larger gauge needles. In most series the overall failure rate varies from 1 to 5%,[4,7-11] but first-year residents have a 10 to 20% failure rate.[4,11]

The overall frequency of dural puncture with larger gauge needles reported in the literature varies from 0.4 to 4%,[4,7-10,12] but there are no reports on the incidence of dural puncture by inexperienced residents. In our patients there were 5 dural punctures, but none of the patients developed headaches. One would anticipate a 9% headache rate with a 22-gauge needle, and a 14% and 18% incidence would be expected with a 20 and 16 gauge, respectively.[13]

Accidental total spinal anesthesia occurs in 0.1 to 0.3% of epidural anesthetics when large-gauge needles are employed.[4,7-12] The incidence may be higher with smaller, 22-gauge needles, though our present series is too small to show this conclusively. We therefore recommend that, following the epidural injection using this technic, the patient be carefully monitored to recognize this complication early and to promptly institute appropriate treatment.

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Correspondence

CALCULATION OF ALVEOLAR OXYGEN TENSION

To the Editor:

I read carefully the paper by Dr. Hewson (57:298-302) on changes in alveolar-arterial O_2 tension gradients with cardiopulmonary bypass. I was unable to find any details of the method used to calculate alveolar O_2 tension, but noted that the respiratory quotient was assumed to be 0.8. It is therefore likely that the standard formula of Riley was used to calculate P_AO_2.

Unfortunately, this formula assumes that there is no exchange of gases other than O_2 and CO_2, and this is most unlikely during N_2O-O_2 anesthesia. In addition, I noted that the system used to ventilate the patients in Dr. Hewson's study allowed partial rebreathing. Consequently even the formula given by Nunn (1963),[1] which does not assume inert gas equilibrium, would not be applicable.

In order to calculate correctly the ideal alveolar O_2 tension, mixed inspired and expired O_2 and CO_2 concentrations would have to be measured. Dr. Hewson states that inspired O_2 concentration was kept at 40%, but I suspect that this would have been the concentration of the fresh gas supply to the circle system. I feel that the conclusions of this study are based upon data which can contain serious errors. Because no absolute values of alveolar or arterial O_2 tensions, nor indeed of alveolar-arterial differences, are given in the article, other more simple analysis of the data is impossible.

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REFERENCE

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To the Editor:

Dr. Drummond suggests that by the use of the Riley formula[1] for the calculation of P_AO_2 in the presence of partial rebreathing and N_2O anesthesia, serious errors in the calculation of $\triangle AaDo_2$ may have occurred in my recently published study of perfusion characteristics during cardiopulmonary bypass (CPB) and $\triangle AaDo_2$.[2] The following discussion will demonstrate that such errors did not occur.

The effect of partial rebreathing upon the P_AO_2 shall be examined first. The respiratory deadspace may be calculated from the following formula:[3]

$$V_d = V_t \left(\frac{Paco_2 - P_Eco_2}{Paco_2 - P_Ico_2}\right) \quad \text{(Eq 1)}$$

In a partial rebreathing circle system with the CO_2 absorber excluded, the P_Ico_2 is determined by the fresh gas flow per minute (FGF), the minute ventilation (MV), and the P_Eco_2.[4] This relationship is expressed as follows:

$$P_Ico_2 = P_{\bar{E}}co_2 \frac{MV - FGF}{MV} \quad \text{(Eq 2)}$$

Therefore:

$$P_{\bar{E}}co_2 = P_Ico_2 \frac{MV}{MV - FGF} \quad \text{(Eq 3)}$$

Substitution of Eq 3 in Eq 1 and solving for P_Ico_2 yields the following:

$$P_Ico_2 = Paco_2 \left[\frac{(V_t - V_d)\ (MV - FGF)}{V_t \cdot MV - V_d\ (MV - FGF)}\right] \quad \text{(Eq 4)}$$

In the case of a 100-kg patient where:

V_t = 1.2 L
MV = 12 L
FGF = 5 L

then

$$P_Ico_2 = \left(\frac{8.4 - 7\,V_d}{14.4 - 7\,V_d}\right) Paco_2 \quad \text{(Eq 5)}$$

With 50 ml/kg/min FGF in a circle system without CO_2 absorption, the P_ACO_2 and by inference the $PaCO_2$ are proportional to the FGF rather than to the alveolar ventilation, so long as MV is greater than FGF.[4] Therefore, during this type of respiratory support, changes in V_d will not significantly alter the $PaCO_2$, but will inversely alter P_ICO_2 according to Eq 5 for a 100-kg patient. Thus P_ICO_2 will fall as V_d rises. Therefore as V_d rises, the P_IO_2 rises. This means that as V_d rises, the real P_AO_2 and the PaO_2 rise while the calculated P_AO_2 remains unchanged. Consequently, as V_d rises there is a decrease in calculated $AaDO_2$ in circumstances where rebreathing is a major determinant of the true P_AO_2. Byrick et al[5] have shown that the physiologic dead space increases with CPB, and the present paper of this author[2] reported that the calculated $AaDO_2$ increases proportionally to the duration of CPB. As this pattern of increased calculated $AaDO_2$ in circumstances which increase V_d is the reverse of that which would be anticipated if partial rebreathing were a major determinant of the true P_AO_2, it must be concluded that partial rebreathing is not a significant factor in the determination of the true P_AO_2 and therefore does not detract from the validity of the calculated $\triangle AaDO_2$.

The second point raised by Dr. Drummond concerns the effect of N_2O exchange on the validity of the calculated $\triangle AaDO_2$, namely the "third gas effect."[5] The greater the duration of CPB, the lower will be the PaN_2O at the end of CPB and, therefore, also 30 minutes after resumption of N_2O-O_2 anesthesia. Therefore, the greater the duration of CPB, the greater the rate of uptake of N_2O at the time of taking the post-CPB arterial blood sample and, therefore, the greater the true P_AO_2 due to the "third gas effect." As a result of the increase in PaO_2 due to the augmented true P_AO_2 but not the calculated P_AO_2, the calculated $\triangle AaDO_2$ would be *inversely* related to the duration of CPB. However, a *direct* rather than an inverse correlation was found between the duration of CPB and the calculated $\triangle AaDO_2$ ($r = +0.63$, $p<0.05$).[2] Thus, inert gas effects do not appear to significantly alter the true P_AO_2, and therefore do not diminish the validity of the calculated $\triangle AaDO_2$.

In conclusion, while agreeing with Dr. Drummond that the effects of partial rebreathing and N_2O shifts on the true P_AO_2 could not be taken into account with the methodology, which was dictated by clinical considerations, it has been shown above that these effects were minimal and therefore do not detract from the validity of the data presented. It is therefore concluded that the direct correlation between (a) $\triangle AaDO_2$ and (b) mean arterial perfusion pressure and duration of CPB and the reciprocal of the body surface area represents a true biological situation, perhaps the development of airway and pulmonary vascular mural edema. These preliminary data draw attention to another direction to be taken in the search for better understanding and prevention of pulmonary dysfunction due to CPB.

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* * *

CARDIAC HERNIATION

To the Editor:

Cardiac herniation following pneumonectomy is a dramatic and potentially fatal complication. The case that Dr. Seltzer presented[1] reminded me of a virtually identical case that my colleagues and I published in this journal in 1972.[2] Since Dr. Seltzer did not include our case in his references, I would like to mention some striking similarities: (1) Both patients underwent right pneumonectomy with a pericardiotomy which was not entirely closed. (2) Both patients sustained cardiac arrest in transit between the operating room and the recovery room. (3) Resuscitation was successful,

the condition remained poor, and a chest x-ray revealed herniation of the heart. (4) Both patients were returned to the operating room for surgical correction, whereupon they experienced dramatic improvement and subsequent recovery.

In my opinion, the primary purpose of such case reports should be to instill within the anesthesiologist a high degree of awareness of potential complications. Without such awareness, prompt diagnosis is much less likely.

Since hundreds of physicians have entered the specialty of anesthesiology during the six years between these reports, I believe that the publication of Dr. Seltzer's case is entirely justified, even though it is repetitious.

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* * *

NEBULIZER CONTAMINATION

The article by Spaepen et al dealing with contaminated nebulizers which appeared in a recent issue of Anesthesia and Analgesia (57:191-196, 1978) raises several questions, especially in the "Materials and Methods" section.

(1) *"All equipment, including the tubing, was sterilized by ethylene oxide prior to being supplied to the patient."* Since both the nebulizers and tubings were gas sterilized, what were the aeration times?[1] They should be varied from material to material. Retention of any residual ethylene oxide would not only be toxic to patients, but would also affect quantitation of bacterial contamination.

(2) *"The equipment remained with the patient for a variable length of time; patients with endotracheal tubes in place received new sterile equipment daily, while in nonintubated patients, the nebulizer was in use for up to 7 days."* This is perhaps a surprising statement. It has been a long-established standard of practice that all-purpose nebulizers be changed every 24 hours,[2-5] perhaps more often on those patients receiving immunosuppressive or broad-spectrum antimicrobial drugs.[4] The contamination of such units is increased by air entrainment[6] when Bernoulli's principle is used for gas dilution. In addition, heating elements set at 37 C may produce an incubatory environment. However, as these temperatures are increased, they become bactericidal.[7]

(c) *"The sampling and plating methods have been described."*[8] A 2-ml aliquot from a reservoir volume of possibly 850 ml is not indicative of the bacterial environment within the entire device. Quantitative and qualitative analyses of the nebulizer reservoir would be more meaningful if larger volumes (50 to 100 ml) were withdrawn and passed through a Millipore filter. Output sampling as described by Ryan and Mihaly[9] is another method for evaluation of nebulizer contamination.

The authors' survey of 600 nebulizers only supports an old axiom: air entrainment and heat support bacterial growth. To glean any other meaningful conclusion from these data is not possible. The authors, in their discussion, indicate that ". . . there must be other factors involved that account for the difference between the 2 nebulizers in contamination rate and elimination of microorganisms." We submit that those "factors" are air entrainment, time in use, and reservoir temperatures. Had these parameters been equated to the "Prevalence of Contamination in Heated Nebulizers During Use by Patients" (table 1) in the study we would find that the majority of contaminated nebulizers was set to deliver 40% O_2. This control will entrain the largest volume of gas for dilution of the O_2. This fact is supported in a previous study by the principle author of this article in which 353 heated nebulizers were sampled.[8] In that study, 118 nebulizers were contaminated, 114 of which were set to deliver 40% O_2. The range of use in that study was from less than 24 hours to 10 days.

In conclusion, this study tells us what we have known for years. Perhaps establishing a standard of use for all-purpose nebulizers, based on contaminant growth, would have been more appropriate here. Furthermore, to indict one brand of nebulizer as being more hazardous than another, based on these

data, is unjust to manufacturers and consumers alike.

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To the Editor:

We offer the following in response to the letter from Alexander and Crowley:

(1) After ethylene-oxide sterilization, all equipment was aerated for 12 hours, in a mechanical aerator, at 50 to 55 C. This is considered sufficient for all types of materials, including plastics.[1] Therefore, we do not feel that any potentially toxic effect for the patients, or influence on subsequent microbial cultures, was at issue.

(2) In nonintubated patients, according to recommendations in the article by Hamrick, Bancroft, Crowley, et al (ref 4 of Alexander and Crowley's letter), daily sterilization of respiratory equipment is not necessary, nor, to the best of our knowledge, is this commonly done in most hospitals.

The effect of water temperature on growth or elimination of bacteria in heated nebulizers is indeed important. We have shown previously,[2] similarly to Crowley's experience,[3] that if water temperature was kept higher than 46 C, the rate of bacterial contamination was reduced in all types of nebulizers studied. However, in our own observations,[2] we have found that the reliability of the thermostats in commercially available heated nebulizers is low, and lower-than-optimal water temperatures were observed frequently in all types of nebulizers. Still, the Ohio nebulizer was least frequently contaminated.

(3) We did not withdraw 2 ml of water, as Alexander and Crowley indicate. In describing our sampling procedure, we mention that water was sampled with a sterile syringe, the needle submerged about 2 cm below the water surface. The volume withdrawn was about 5 ml. Anyway, the overwhelming majority of our positive cultures gave concentrations of more than 1000 colonies/ml. Therefore, the size of the sample withdrawn could not have been an important issue.

Alexander and Crowley claim that, in our previous publication,[2] 114 out of 118 contaminated nebulizers were set to deliver 40% O_2. It is not obvious to us what this statement is based upon; in our paper we did not specify the nebulizer settings for delivery of O_2 concentration.

Finally, our conclusion about the differences in resisting or eliminating microbial contamination is based not only upon the cultures of water sampled from heated nebulizers in use by patients, but also on an experimental part of the study that dealt with the survival and elimination of microorganisms inoculated into various types of nebulizers. In this, there was a clear-cut difference among the various equipments studied, as described in our paper.

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* * *

ANESTHETIC CIRCUITS AND INFLOW REQUIREMENTS

To the Editor:

The current dialogue which has appeared in these pages and elsewhere about the merits or demerits of anesthesia circuits of particular design, and about rates of fresh gas inflow that would or should ensure total removal of CO_2, appears to miss the point and muddle the issue.

The factors that control the rate of carbon dioxide accumulation and removal are (1) the rate of carbon dioxide entry into the system, (2) the total volume of the system into which it is delivered, (3) that fraction of the system which is exchanged at each "pass", and (4) the number of such "passes" per minute. Equations for the prediction of present or future states of the system, given arbitrary constraints for any of the variables, are available and they belong to the general class of equations for solving problems in the areas of (1) continuous dilution processes, (2) compartment analysis from tracer substance distribution, (3) rate of disappearance of particulate or thermal pollutants, etc.

The ponderous rewriting of these equations by means of subscripted or superscripted symbols and the invention of new appellatives (ie, "wasted ventilation"[1]) confound, rather than simplify, the issue. As for mechanical models, such items have been used for the purpose of generating publishable material for a long time,[2,3] and little is gained by beating such a tired horse. To argue about the relative merits of various rates of fresh gas inflow into the system betrays a naivete and a belief *in the power of the right formula* which is somewhat alarming.

Pragmatically, and considering the wide range of normal values for CO_2 production and for ventilatory exchange, the issue can be reduced to two objectives: (1) oxygenation of the patient, and (2) knowledge of CO_2 distribution within the system. Both objectives are reasonably simple to achieve.

Adequate oxygenation of arterial blood throughout anesthesia can be achieved via early denitrogenation followed by avoidance of N_2O,[4] which sequence would offer further protection: (1) in the event of hypoventilation, adequate oxygenation is still maintained by virtue of the "apneic oxygenation" phenomenon,[5] and (2) the high P_{O_2} in the inspired mixture is capable of overcoming the effects of those disturbances in ventilation/perfusion ratio which occur during anesthesia (their severity may be estimated by observing that on many occasions the arterial P_{O_2} is in the range of 70 to 80 torr at a time when the inspired mixture may contain as much as 50% O_2).

Knowledge of the CO_2 distribution can be acquired by measuring and recording in a continuous manner its concentration in the gas mixture as it enters and leaves the patient. The technic is simple and reliable, it has been previously published,[6] and appropriate instrumentation is readily available.

In conclusion, rather than engage in futile doctrinaire arguments about what should be or might be going on, we should spend time, efforts, and money toward the development of anesthetic systems such that the management can be conducted on the basis of factual data generated within the system and in real time.

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* * *

MORE ON DENTISTS AND ANESTHESIOLOGY

To the Editor:

I would like to respond to one question and the associated answers published in the Jan-Feb 1978 issue (pages 148-149). The question regarded the legality of the training in and subsequent practice of anesthesia by licensed dentists in the United States.

I generally concur with Dr. Eastwood's thoughtful comments. I would, however, like to comment on Dr. North's answer. Three "problems" with the training of dentists in anesthesiology were cited. As Dr. North indicated, the educational deficit in clinical medicine can be overcome by selecting dentists that are highly motivated and intellectually capable of the challenge. The second problem Dr. North discussed is one with which I am concerned. In effect, the activities of individuals with little anesthesia training or training of poor quality lower the quality of patient care and undermine the development of anesthesia as a specialty. Both medically and dentally trained individuals are responsible for this problem. However, there exists a first step toward a solution to this problem as it regards dentally trained individuals. Dr. North indicated that ". . . there is no national accrediting or certifying mechanism for such individuals, which precludes any estimate of their qualifications by hospital staffs, physicians, or patients." In fact, the American Dental Society of Anesthesiology does administer a fellowship examination which is valuable for estimation of credentials.

I wanted to make the above comments because I and others believe dentists have neglected the area of pain and anxiety control for too many years. Drs. Wells and Morton were dentists sensitive and intelligent enough to make great contributions to pain and anxiety control in the mid-1800's. Since that time, very few dentists have been able to contribute to this important but relatively neglected area of patient care. I believe that lack of adequate training has been primarily responsible for the relative inactivity on the part of dentists in this important endeavor.

Anesthesiology, in my opinion, is the educational avenue best suited for the development of knowledge and skill necessary for the study of pain and anxiety control. A number of physician-anesthesiologists chairing academic departments in the United States have become aware of the great need in dentistry for academic personnel to direct research and educational efforts. I am grateful for the dedication of these far-sighted individuals. I hope Dr. North and his colleagues at the University of Tennessee might reconsider dentally trained applicants to their residency in light of the great opportunities and needs for dentists with training in anesthesia.

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Book Reviews

Pain - New Perspectives in Measurement and Management, edited by A. W. Harcus, R. Smith, and B. Whittle, 194 pp. $23.50, New York, Churchill Livingstone, 1978.

This book is based on a two-day Symposium held in May of 1977, in England. This Symposium was centered around the introduction of a new narcotic analgesic agent "buprenorphine." The first 136 pages represents a collection of papers loosely focused around the topics of; the psychological, physiological and pharmacological aspects of pain and the assessment of narcotic analgesics. The remaining 48 pages discusses, in some detail, the pharmacology and clinical trials of the new narcotic analgesic buprenorphine, which has recently been introduced for general usage in Great Britain.

Overall the text has a heavy pharmacological leaning. In the opening chapter, a physician, Ian Donald, relates his personal experience with three open heart surgeries. The insightful descriptions of post-operative pain and recovery serve as a vivid background on which to discuss the various psychological, situational and hurt aspects of human suffering. As a personal experience, this chapter may be too readily neglected and considered non-scientific. But, to the careful and sensitive reader there is great value in perceiving pain from the viewpoint of the sufferer and not the manager of pain, who is handling the problem in some more remote abstract manner.

The remainder of the first part of the text deals with the assessment of pain, its measurement and interpretation of the measurements. Here are detailed; the use of nurse observers, the measurement of pain by comparison and patient's requests for medication, and the interpretation of the numbers obtained during measurement. These papers are of some value and in essense represent an all too brief review of the existing literature.

The next chapter represents a collection of unrelated papers concerning the measurement of the effect of narcotic agents and other strong analgesics on the ureter, respiratory and cardiovascular systems. The discussion in this chapter serves little purpose in integrating these separate areas.

A brief section with a strong pharmacological orientation discusses, all too briefly, the problems associated with strong analgesics and pharmacological advances in the development and testing of analgesic agents. These are of little clinical value and essentially serve as a review of the side effect of narcotic agents. This is followed by a similarly brief review of the problems of dependency and abuse potential of the narcotic analgesics.

Another session of the meeting is reproduced containing material concerning the analgesic management of the pain of; myocardial infarction, post-operative pain and the pain of acute trauma. Again, these chapters have a heavy pharmacological orientation and are relatively limited in their scope to be of any clinical or research value.

The remainder of the text is specifically concerned with the new analgesic agent buprenorphine. Five independent clinical studies of patients with acute pain, primarily of a post-surgical nature, are presented together with the manufacturer's detailed studies of the drugs effect on normal human subjects. These reports reveal that buprenorphine has an analgesic potency 20-50 times that of morphine and provides effective analgesia for from 4-10 hours or more following parental administration. It is stated that the mild respiratory and cardiovascular depression, seen in healthy volunteer subjects, was less than that to be expected with equal analgesic doses of morphine. Mild sedation was found to be common and it was concluded that buprenorphine has a relatively low physical dependence potential. It appears from the material here that buprenorphine may represent a significant improvement in narcotic analgesia.

This book has a variety of shortcomings,

most of which are a result of using materials prepared for symposia and conferences. The chapters are only loosely related to each other and vary greatly in quality. There is no logical flow or overall integration of the subject manner. Several of the chapters, including the one mentioned above concerning the physician's personal experience with pain, and another on care and terminal illness, while standing as individual essays, bear little relation to the overall theme of the text.

In summary: This book does a bearly adequate job of reviewing, from a pharmacological viewpoint, the clinical pharmacology of narcotic agents and presents preliminary data on a new agent. The title and the cost of the book, however, imply that more is to be received for the relatively high price paid.

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* * *

Handbook of Clinical Pharmacology, by Felix Bochner, George Carruthers, Jens Kampmann and Janice Steiner, 313 pp, $9.95, Boston, Little, Brown and Company, 1978.

This handbook is intended to provide a critical and rational approach to the prescribing of drugs. That objective is different from a number of handbooks available to physicians. In most instances, the handbooks provide a large base of factual information without an attempt to convey much information about fundamental principles of drug action, drug metabolism, drug elimination, and the various effects of disease states, pregnancy, altered metabolic rate, age and other factors which may alter therapeutic responses to drugs. In the first ten chapters, the authors have succeeded admirably in introducing the reader in a highly condensed form to many of these aspects of drug therapy with specific examples of situations where disease or other factors may alter therapeutic response.

The first ten chapters comprise approximately 30% of the handbook. The remaining 70% of the book (200 pages) is included in Chapter 11 entitled "Drug Profiles." Chapter 11 contains the type of factual information usually presented in a handbook of drug therapy and alluded to above. The authors, unfortunately, have elected to present Chapter 11 in alphabetical order of drug name rather than by therapeutic indication, pharmacologic action, or other more easily assimilated and useful manner of arrangement. Comparison of drugs within a group having similar pharmacologic actions is made more difficult when one sifts through mixtures of antibiotics, cardiotonics, diuretics, sedatives, etc.

In summary, this handbook, in the first ten chapters, provides useful information in appropriately condensed form concerning the rational basis for drug therapy and those factors which may alter therapeutic effects. The last chapter, containing the bulk of factual information about commonly used drugs, is useful for the information presented on individual drugs, but is presented in alphabetical order. This arrangement of the last chapter (about 70%) of the printed material in the book, leaves much to be desired and the reader is forced to thumb through various parts of the book in order to gain information about drugs having similar actions or acting on specific organ systems. This disadvantage is particularly distracting in a handbook approach where readers seek information quickly and easily. If the latter two-thirds of the book could be divided into a number of shorter chapters dealing with drugs arranged by pharmacologic action, therapeutic effect, or organ system, this handbook would be exceedingly more useful.

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Anesthesia AND Analgesia

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AIR EMBOLI
EVEN DURING
ELECTROCAUTERY
USE

NEW

MEDA SONICS

MODEL P81 PROBE
AND VERSATONE
DOPPLER MODEL D8

Now dramatically reduces
interference from
electrocautery equipment.

The Model P81 probe is designed to detect venous embolism during any surgical procedure in which is is a potential complication. This probe and the ERSATONE® Doppler are now manufactured ing special shielding techniques to substantially luce electrocautery interference. This permits anesthesiologist to continue monitoring Dop- r sounds of heart motion even while the electro- utery is being used.

e potential complication of venous air embolism s received considerable recognition in the lit- ture. Michenfelder, et. al.(1), have recommended ly diagnosis as the most effective means of venting serious sequelae from air embolism ing neurosurgical procedures performed in the ight position. The Model P81 probe provides a ntinuous Doppler signal which varies in audible h in response to heart and blood flow motion. tinctive, abrupt changes from the normal nds are caused by emboli. A tape cassette ording is available on request from MedSonics.

Michenfelder, J.D., et. al., "Evaluation of an Ultra- c Device (Doppler) for the Diagnosis of Venous Air olism." Anesthesiology, 36, 2 (February 1972).

UTIONS AND CONSIDERATIONS – The asound method of air embolism detection is ect to both false positive and false negative cations. It should not be the only step taken iagnose venous air embolism.

TERCHANGEABLE PROBES

P81 probe is one of a family of probes made use with the MedSonics VERSATONE® Dop- instruments. It is easily interchangeable with r probes manufactured for this instrument.



P82/P83

The Model P82 and P83 Doppler ultrasound pencil-shaped probes may be used transcutaneously to detect blood flow or intraoperatively to examine flow in vessels exposed during surgical procedures.

P84

The Model P84 probe is designed for use in monitoring blood flow on the principal blood vessels of the arms or legs. It is possible to take systolic blood pressures even in hypotensive patients in conjunction with a cuff and manometer.

FOR MORE INFORMATION CONTACT

MEDA SONICS

P.O. Box M (340 Pioneer Way), Mountain View, CA 94042
Toll free telephone: 800 227-8076
In California call collect: (415)965-3333
Telex: 33-4448 Cable: MEDASONICS

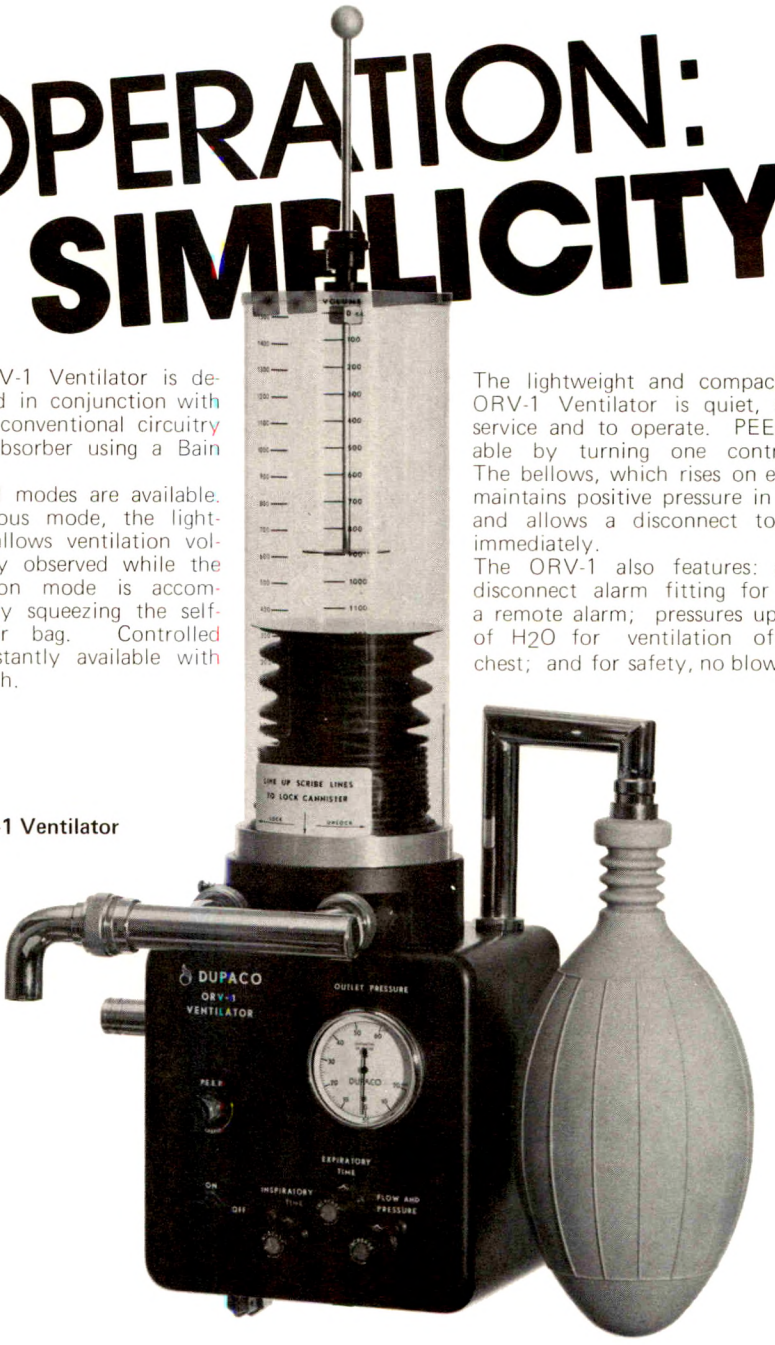
OPERATION: SIMPLICITY

The Dupaco ORV-1 Ventilator is designed to be used in conjunction with an absorber and conventional circuitry or without an absorber using a Bain type circuit.

Three operational modes are available. In the spontaneous mode, the lightweight bellows allows ventilation volume to be easily observed while the assisted ventilation mode is accomplished by simply squeezing the self-inflating reservoir bag. Controlled ventilation is instantly available with the turn of a switch.

The lightweight and compact Dupaco ORV-1 Ventilator is quiet, simple to service and to operate. PEEP is available by turning one control knob. The bellows, which rises on exhalation, maintains positive pressure in the lungs and allows a disconnect to be seen immediately.

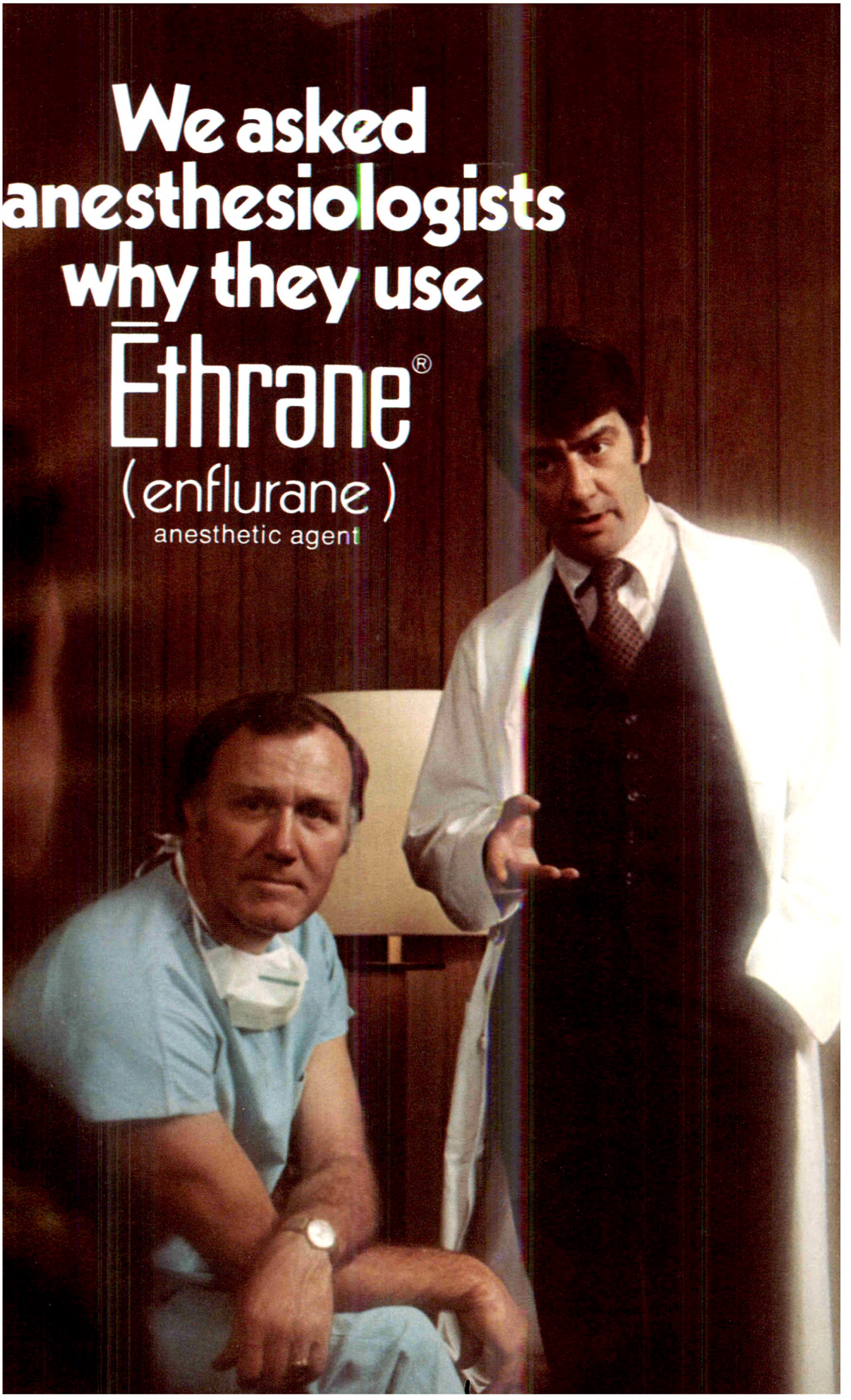
The ORV-1 also features: a built-in disconnect alarm fitting for use with a remote alarm; pressures up to 80cm of H_2O for ventilation of the stiff chest; and for safety, no blow-off valve.



The Dupaco ORV-1 Ventilator

DUPACO

Post Office Box 98, San Marcos, Calif. 92069


We asked anesthesiologists why they use
Ethrane®
(enflurane)
anesthetic agent

"Why do we use Ēthrane® (enflurane)?"

"When you have an anesthetic agent like Ēthrane which you can so predictably control—and it gives you muscle relaxation —that's a real advantage."†

Muscle relaxation with ĒTHRANE (enflurane) usually is sufficient for lower and many upper abdominal procedures at normal levels of anesthesia. Should greater relaxation be required, the ability of ĒTHRANE (enflurane) to potentiate the action of nondepolarizing agents permits significantly reduced dosage of these agents. This property of ĒTHRANE (enflurane) may be particularly useful when supplemental relaxation is required toward the end of surgery.

"When patients wake up following Ēthrane and demonstrate that they have control of their airway, and they have a satisfactory ventilatory exchange, I can send them back to a less controlled environment, with less monitoring, and feel comfortable."†

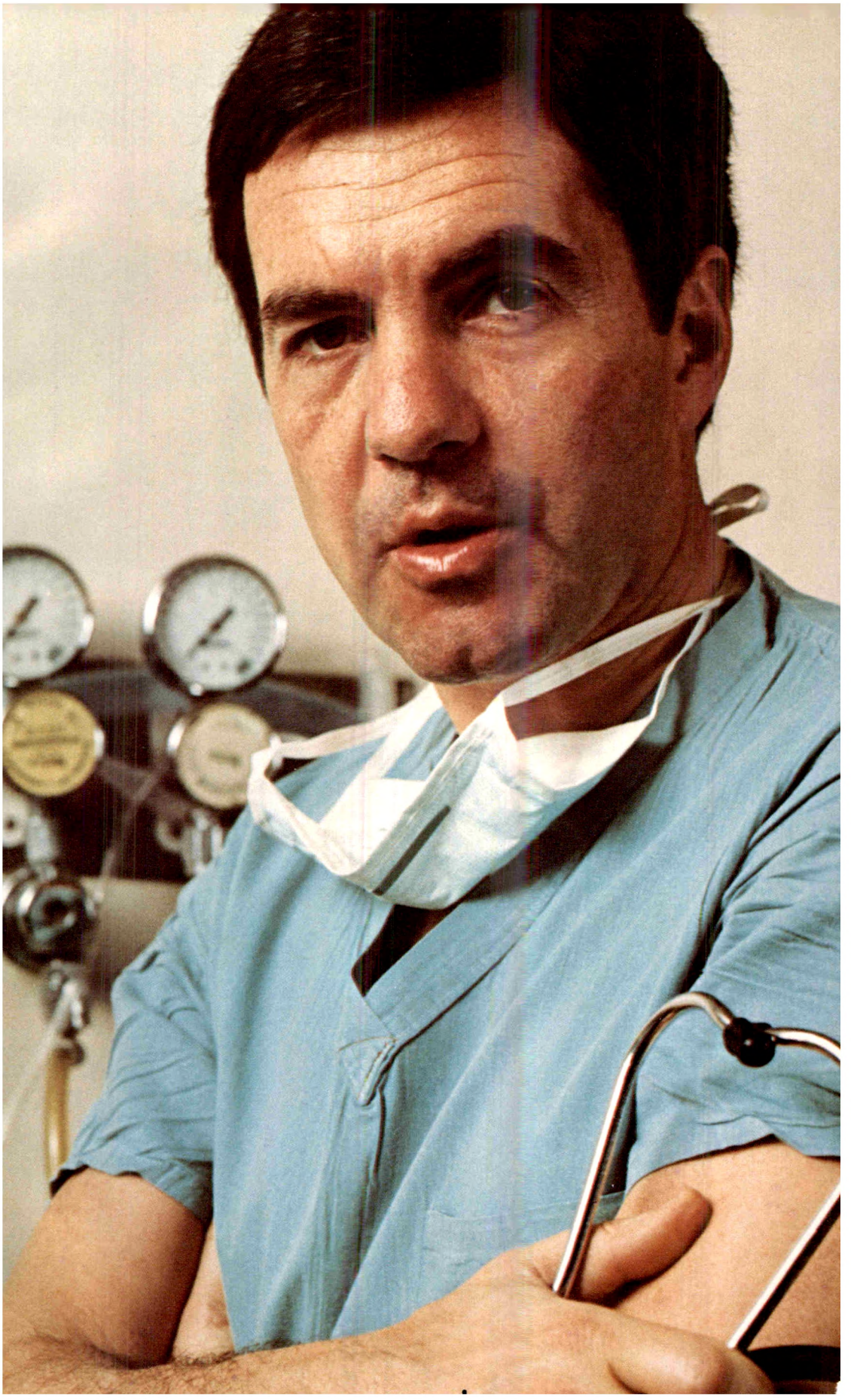
The low blood solubility of ĒTHRANE* (enflurane) provides for its prompt elimination following surgery. Patients usually remain sedated for 10 to 20 minutes, then waken smoothly and rapidly with little or no postanesthetic effect. Vital signs return to preanesthetic levels promptly and patients are generally alert, without nausea and able to take fluids by mouth.

*Blood/gas partition coefficient: 1.9 @ 37°

†Excerpts from taped interview, anesthesiologist in Philadelphia, Pa., on file, Ohio Medical Products.

Please see following page for complete product use information.

Ohio Medical Products

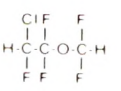


Ethrane® (enflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription

DESCRIPTION

ETHRANE (enflurane) is a nonflammable inhalation anesthetic agent. It is 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether, molecular weight 184.5, and its structural formula is:



The boiling point is 56.5°C at 760 mm Hg, and the vapor pressure (mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C. Vapor pressures can be calculated using the equation

$$\log_{10}P = A + B/T \quad A = 7.967 \quad B = -1678.4 \quad T = {}^{\circ}C + 273.16 \text{ (Kelvin)}$$

The specific gravity (25°/25°C) is 1.517. The refractive index at 20° is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C. The M.A.C. (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70% nitrous oxide and oxygen, and 1.17 in 30% nitrous oxide and oxygen.

ETHRANE is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No chemical stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary to maintain stability even in the presence of ultraviolet light. ETHRANE is stable to strong base and does not decompose in contact with soda lime and does not attack aluminum, tin, brass, iron or copper. The partition coefficients of ETHRANE at 25°C are 74 in conductive rubber and 1.20 in polyvinyl chloride.

ACTIONS

ETHRANE (enflurane) is an inhalation anesthetic. Induction and recovery from anesthesia with ETHRANE are rapid. ETHRANE has a mild, sweet odor. There is mild stimulus to salivation or tracheobronchial secretions when ETHRANE is used alone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia changes rapidly with ETHRANE. ETHRANE reduces ventilation as depth of anesthesia increases. High pCO_2 levels can be obtained at deeper levels of anesthesia if ventilation is not supported. ETHRANE provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during ETHRANE anesthesia. ETHRANE anesthesia has been used in excision of pheochromocytoma in man without ventricular arrhythmias. On the basis of studies in patients anesthetized with ETHRANE and injected with epinephrine containing solutions to achieve hemostasis, up to 10 ml of 1:100,000 or 1:200,000 epinephrine containing solution may be injected subcutaneously at a rate of not more than 10 ml per minute and no more than 30 ml per hour. All customary precautions in the use of vasoconstrictor substances should be observed.

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with ETHRANE. THE NONDEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED. In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height. Neostigmine does not reverse the direct effect of ETHRANE.

Biotransformation of ETHRANE in man results in low levels of serum fluoride ions averaging 15 mM/L. These levels are well below the 50 mM/L threshold level which can produce minimal renal damage in normal subjects; however, it is possible that these levels could result in damage in patients with severely impaired renal function or those undergoing renal transplantation. Depression of lymphocyte transformation does not follow prolonged ETHRANE anesthesia in man in the absence of surgery. Thus ETHRANE does not depress this aspect of the immune response.

INDICATIONS

ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Seizure disorders (see WARNINGS).

Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics.

WARNINGS

Increasing depth of anesthesia with ETHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentration usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental function testing does not reveal any impairment of performance following prolonged ETHRANE anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

The action of nondepolarizing relaxants is augmented by ETHRANE. Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from myoneural blockade will be longer in the presence of ETHRANE than for other commonly used anesthetics.

Usage in Pregnancy: Safety in pregnancy has not been established. Reproduction studies have been performed in rats and rabbits, and there is no evidence of harm to the animal fetus. The relevance of these studies to the human is not known. Since there is no adequate experience in pregnant women who have received the drug, safety in pregnancy has not been established.

PRECAUTIONS

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. ETHRANE (enflurane) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug. As with other general anesthetics and some muscle relaxants, hyperpyrexia has been observed with the use of ETHRANE.

ADVERSE REACTIONS

1. Motor activity exemplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia, or light levels with hypocapnia.
2. Hypotension and respiratory depression have been reported.
3. Arrhythmias, shivering, nausea, and vomiting have been reported.
4. Elevation of the white blood count has been observed.

DOSAGE AND ADMINISTRATION

The concentration of ETHRANE (enflurane) being delivered during anesthesia from a vaporizer should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for ETHRANE.
b) vaporizers from which delivered flows can easily and readily be calculated.

Nothing is present in the agent to alter calibration or affect the operation characteristics of the vaporizer.

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ETHRANE and the heart rate remains constant. The use of anticholinergic drugs is a matter of choice.

Induction: Induction may be achieved using ETHRANE alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the ETHRANE mixture. In general, inspired concentrations of 3.5-4.5% ETHRANE produce surgical anesthesia in 7-10 minutes.

Maintenance: Surgical levels of anesthesia may be obtained with 1.5-3% ETHRANE. Maintenance concentrations should not exceed 3%. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of ETHRANE concentration in the absence of other complicating problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Overdosage: In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration; establish that the airway is clear and initiate assisted or controlled ventilation with pure oxygen as circumstances dictate.

PACKAGING

ETHRANE (enflurane) is packaged in 125 and 250 ml amber colored bottles.

Ohio Medical Products
Division of Airco Inc.
P.O. Box 7550, 3030 Airco Drive, Madison, Wis. 53707

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The BEAR® 1 Adult Ventilator

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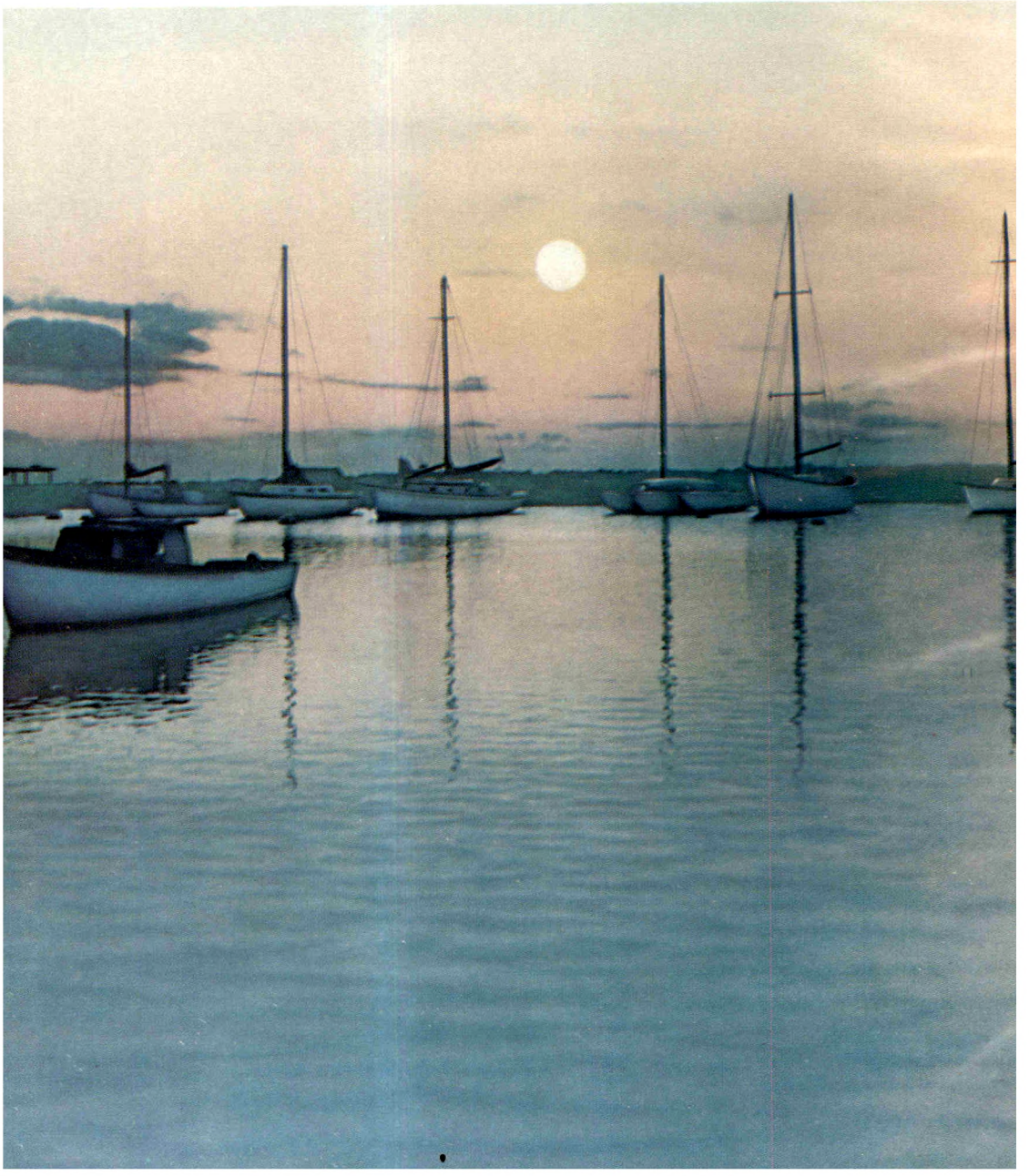
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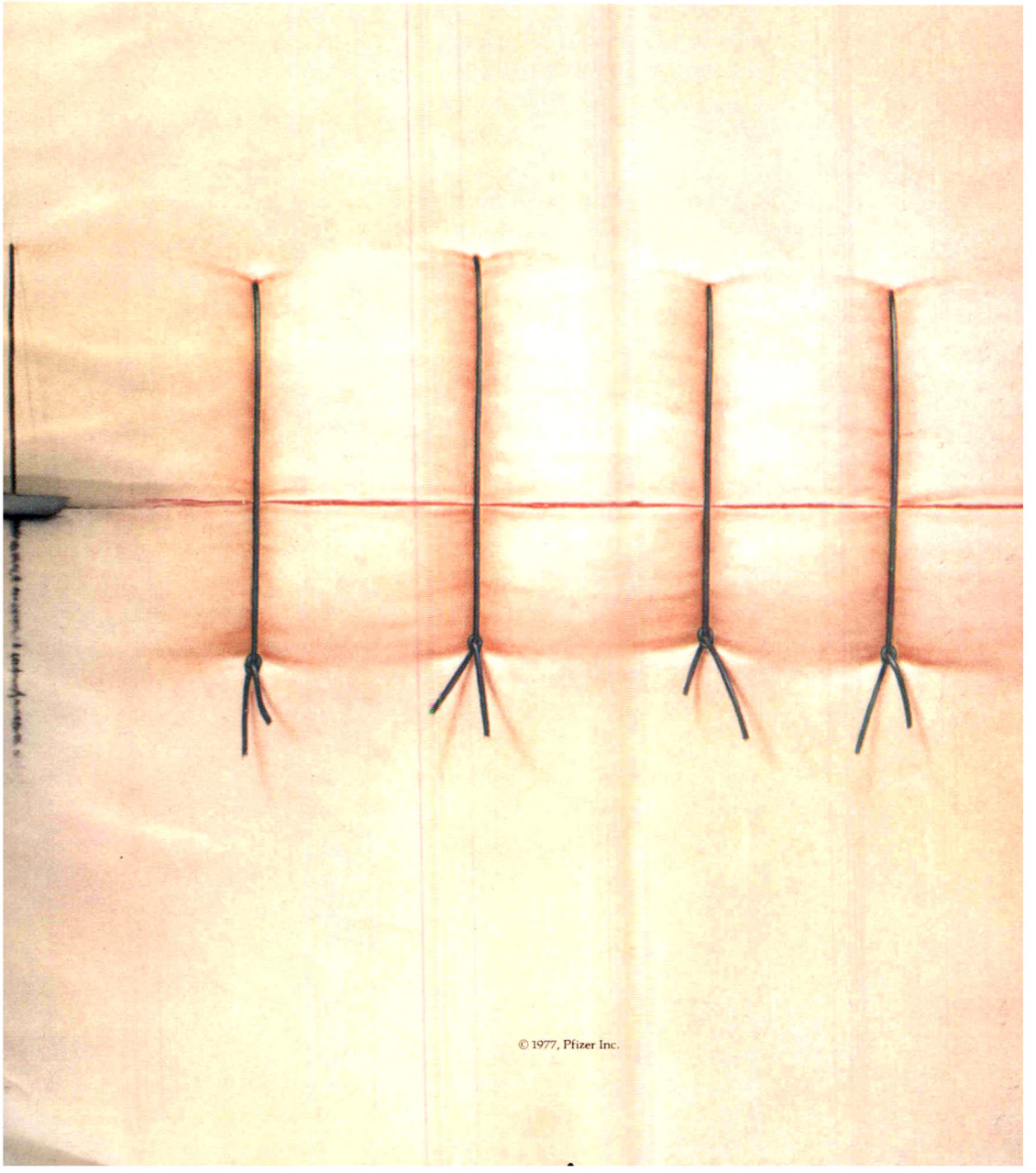


Vistaril® I.M.
(hydroxyzine HCl)

—allays anxiety
—reduces narcotic requirements
—and controls emesis

surgery

Please see Brief Summary on following page for contraindications, precautions and adverse reactions.



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Vistaril® I.M.
(hydroxyzine HCl)

100 mg/2 ml—50 mg/ml and
25 mg/ml Vials and Isojects®

preoperatively and postoperatively

allays presurgical anxiety...allays the anxiety that may heighten the perception of postoperative pain

may enhance the effects of analgesics and reduce narcotic requirements

controls postoperative emesis

vital signs are seldom impaired (Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.)

BRIEF SUMMARY

ISTARIL® (hydroxyzine hydrochloride) Intramuscular Solution
or Intramuscular Use Only

ontraindications: Hypersensitivity to hydroxyzine. The solution is or intramuscular use only and should not, under any circumstances, e injected subcutaneously, intra-arterially, or intravenously.

Hydroxyzine, when administered to the pregnant mouse, rat, and abbit, induced fetal abnormalities in the rat at doses substantially ove the human therapeutic range. Since adequate data are not vailable to establish safety in early pregnancy, hydroxyzine is ontraindicated during this period.

recautions: HYDROXYZINE MAY POTENTIATE THE ACTION OF CENTRAL NERVOUS SYSTEM DEPRESSANTS SUCH AS NARCOTICS AND BARBITURATES. In conjunctive use, dosage for hese drugs should be decreased as much as 50%. Because drowsiness ay occur, patients should be cautioned against driving a car or perating dangerous machinery. The usual precautions for intra-uscular injection should be followed; soft-tissue reactions have rely been reported when proper technique has been used. Hydrox-zine intramuscular solution should be injected well within the body f a relatively large muscle. Inadvertent subcutaneous injection may sult in significant tissue damage. In adults, the preferred sites are he upper outer quadrant of the buttock (i.e., gluteus maximus), or he mid-lateral thigh. In children, preferably the mid-lateral muscles f the thigh. In intants and small children, the upper outer quadrant f the gluteal region should only be used when necessary, as in burn atients, in order to minimize the possibility of damage to the sciatic erve. The deltoid area should be used only if well developed, such s in certain adults and older children, and then only with caution to void radial nerve injury. Intramuscular injections should not be ade in the lower and middle thirds of the upper arm. Aspiration is ecessary to help avoid inadvertent intravascular injection.

dverse Reactions: Drowsiness may occur; if so, it is usually transi-ory and may disappear in a few days of continued therapy or upon osage reduction. Dryness of the mouth may occur with higher oses. Involuntary motor activity, including rare instances of tremor nd convulsions, has been reported, usually with doses considerably igher than those recommended.

upply: Vistaril (hydroxyzine HCl) Intramuscular Solution: 5 mg/ml—10 ml vials; 50 mg/ml—2 ml and 10 ml vials; Isoject®, 5 mg/ml and 50 mg/ml—1 ml fill; 100 mg/2 ml—2 ml fill.
Military Depot: NSN 6505-00-052-1367 (50 mg/ml, 10 ml vials)
VA Depot: NSN 6505-00-052-1367B (50 mg/ml, 10 ml vials)
lore detailed professional information available on request.

Pfizer
LABORATORIES DIVISION
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International Anesthesia Research Society

MARCH 11-15, 1979

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AND
COUNTRY CLUBS

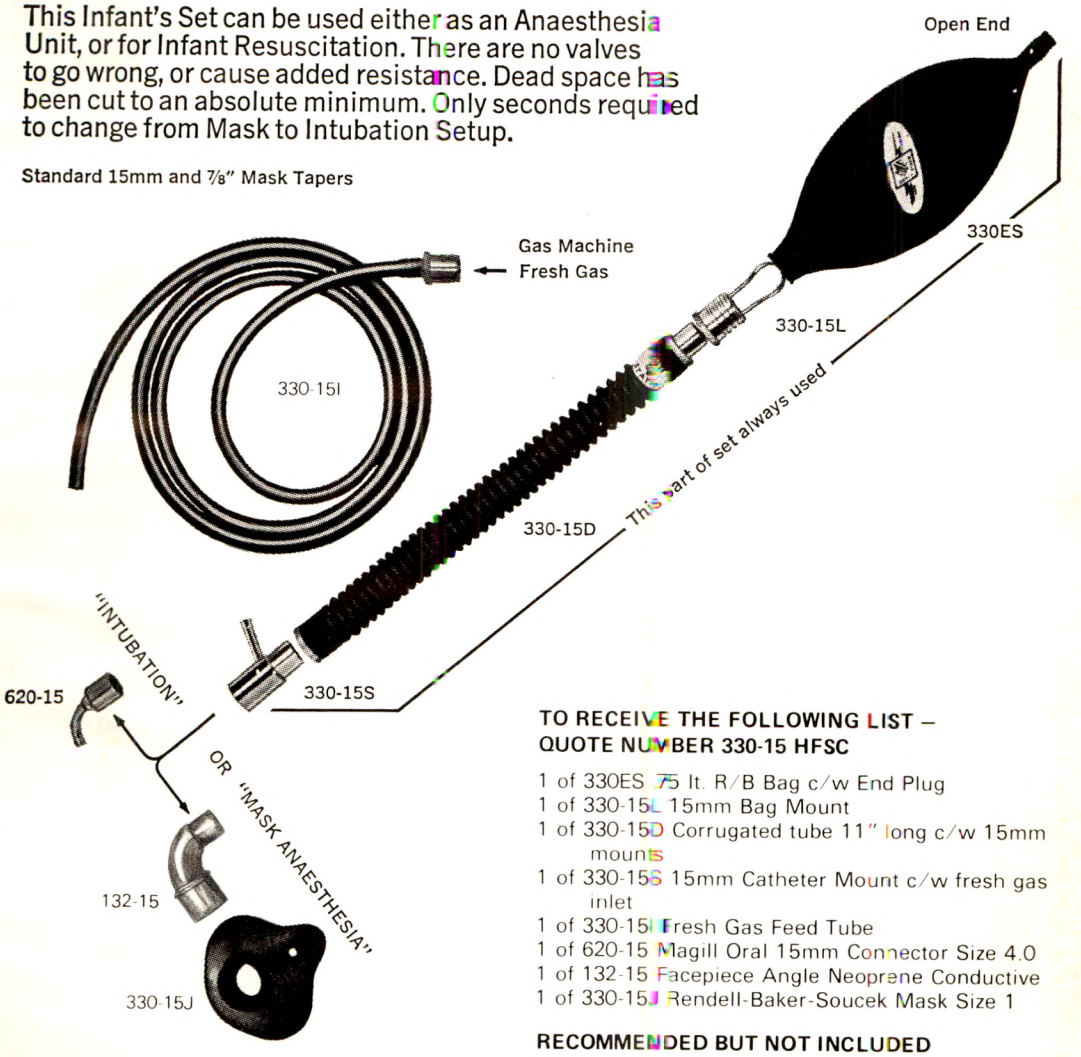
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as used by leading children's hospitals

This Infant's Set can be used either as an Anaesthesia Unit, or for Infant Resuscitation. There are no valves to go wrong, or cause added resistance. Dead space has been cut to an absolute minimum. Only seconds required to change from Mask to Intubation Setup.

Standard 15mm and 7/8" Mask Tapers



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1 of 620-15 Magill Oral 15mm Connector Size 4.0
1 of 132-15 Facepiece Angle Neoprene Conductive
1 of 330-15J Rendell-Baker-Soucek Mask Size 1

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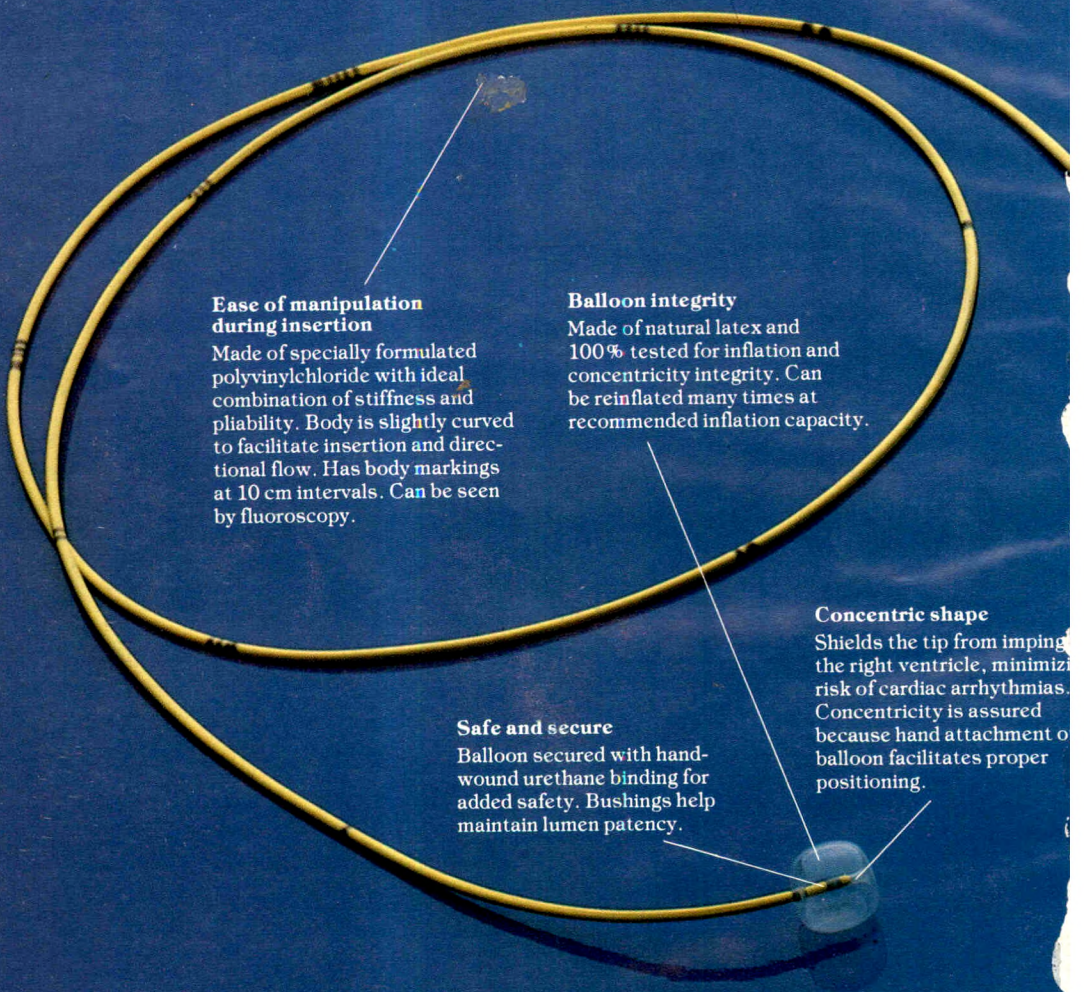
6 (1 each) 674/330 Foregger Coles Tubes 8 to 18 F.G.
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1 330LC Leather Case
1 of 330-15D Corrugated tube c/w 15mm mounts.

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Made of specially formulated polyvinylchloride with ideal combination of stiffness and pliability. Body is slightly curved to facilitate insertion and directional flow. Has body markings at 10 cm intervals. Can be seen by fluoroscopy.

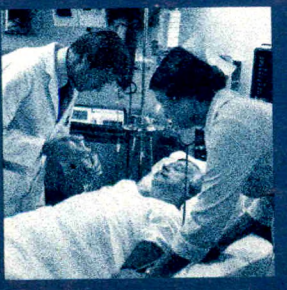
Balloon integrity
Made of natural latex and 100% tested for inflation and concentricity integrity. Can be reinflated many times at recommended inflation capacity.

Concentric shape
Shields the tip from imping the right ventricle, minimizi risk of cardiac arrhythmias. Concentricity is assured because hand attachment o balloon facilitates proper positioning.

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Balloon secured with hand-wound urethane binding for added safety. Bushings help maintain lumen patency.

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The reasons? More clinical experience (over one-half million inserted), hundreds of published papers in the medical literature, unsurpassed manufacturing quality (15 separate quality control checks) meticulous hand-



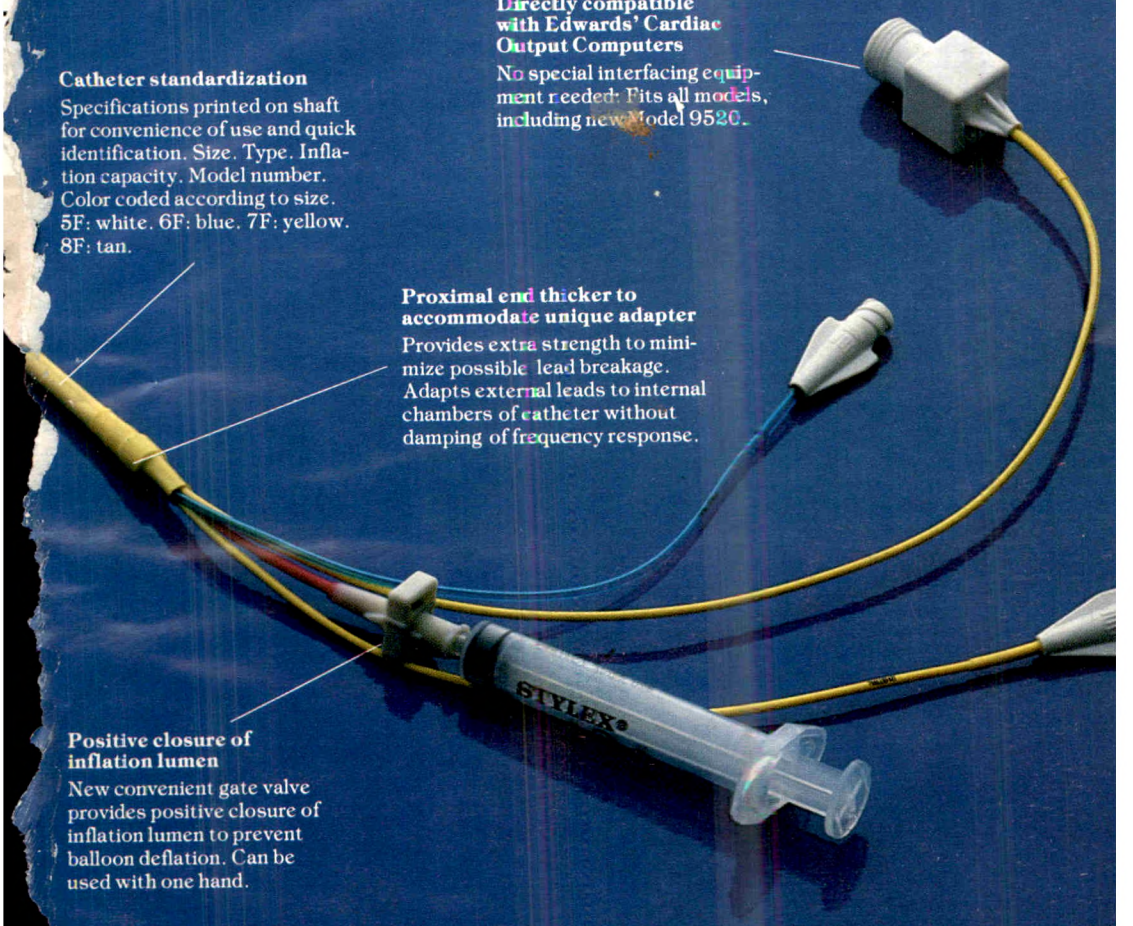
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No special interfacing equipment needed. Fits all models, including new Model 9520.

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New convenient gate valve provides positive closure of inflation lumen to prevent balloon deflation. Can be used with one hand.

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Simple, Functional, Logical...Look into It.

Look into a Curity spinal anesthesia tray. You'll see all the essential components for a safe, efficient spinal anesthesia procedure presented in their logical order of use. The generous CSR wrap unfolds into a large fluid-resistant sterile field. A fluid-proof underpad, lift-out prep deck and long-handled prep applicators facilitate patient preparation. The clear plastic splash shield protects the procedural components from contamination during patient prep. For secure positioning, the patented fluid-resistant fenestrated drape has extra large adhesive tabs.



You'll find only the highest quality components in Curity spinal anesthesia trays, including the exclusive use of Becton Dickinson needles and syringes. The spinal needles and stylets are sharpened together to assure an exact fit for minimal trauma on insertion. The syringes are precisely calibrated with the plungers matched to the barrels for smooth, even control. There's even a Curad adhesive bandage to dress the wound after the procedure.



A choice of nine different trays allows you to select the essentials you need for each patient and procedure.



The Curity spinal anesthesia tray...look into it.

A drug insert sheet will give you detailed information on precautions, contraindications and adverse reactions.

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